UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

DATE: XX X, 2020

SUBJECT: **Dicamba: Tier II Incident and Epidemiology Report**

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Summary and Conclusions

This memorandum is the Dicamba Tier II Incident and Epidemiology Report. Prior to this memorandum, dicamba incidents were reviewed in November 2015 (E. Evans and S. Recore, D427231, 11/10/15). In 2015, the Health Effects Division (HED) prepared a preliminary Tier I (scoping) human incident review of dicamba human incident reports by consulting the Office of Pesticide Programs (OPP) Incident Data System (IDS) and Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH) Sentinel Event Notification System for Occupational Risk-Pesticides (SENSOR) for reports of poisoning incidents. In 2015, the incident memo stated that "a relatively high frequency of cases reported for dicamba in both IDS and SENSOR-Pesticides. While the majority of case reports are low in severity in both databases, there are a number of moderate severity cases reported. Further review of dicamba may be warranted."[1]

For this Dicamba Tier II Incident and Epidemiology Report, HED found that overall, the majority of dicamba incidents were low in severity (84% in IDS, 86% in SENSOR-Pesticides, NPIC 69%). IDS, SENSOR-Pesticides and PISP identified that most incidents involved homeowners exposed either when applying the product or through spills/splashes of the product. Most often these exposures were to lawncare products with more than one active ingredient. In addition, postapplication exposure to non-applying members of the household following application were reported. Among the occupational exposures to dicamba, these too primarily involved exposures while applying the pesticide, several of these involved application equipment failures; secondly several agricultural workers were directly hit with the pesticide spray during an active pesticide application. Across all four incident databases reviewed, there was a total 29 of spray drift-related exposures. Dicamba cases often reported adverse dermal, respiratory, and gastrointestinal health effects. Many cases also reported adverse gastrointestinal and ocular health effects.

Commented [EE1]: This is the dicamba conclusion- I deleted out the DDVP incident language- I did not delete anything DDVP epi at all

In order to assess the epidemiologic evidence on the potential adverse effects of dicamba exposure, HED performed a systematic review of the epidemiologic literature on dicamba and identified 78 articles that investigated a range of health outcomes, including 33 studies on carcinogenic health outcomes and 45 on the non-carcinogenic outcomes Parkinson's Disease, respiratory effects, thyroid disease, and a range of other health outcomes. While there were some individual studies identified that reported a positive association between dicamba exposure and some adverse health effects, the overall evidence was based on a small body of studies (i.e., typically only one or two study populations per health outcome) that often had substantive limitations with respect to their study design, exposure assessment approach and outcome assessment approach. As such, HED concluded that overall, there was insufficient epidemiologic evidence to suggest a clear associative or causal relationship exists between dicamba exposure and the adverse health effects examined in the available epidemiologic literature. The Agency will continue to monitor the epidemiology data and -- if a concern is triggered -- additional analysis will be conducted.

[1] For this review, no medical case reports were investigated.

1 BACKGROUND

Dicamba is a widely used herbicide on agricultural crops, fallow land, pastures, turfgrass, and rangeland. Dicamba is a benzoic acid. Dicamba is used for control of emerged broadleaf weeds and provides some residual control of germinating weeds.

HED is currently re-evaluating the toxicity, exposure, and risk profile of dicamba under the Food Quality Protection Act (FQPA)-mandated Registration Review program. The registration review program is designed to ensure EPA evaluates new information regarding pesticides on a 15-year cycle, and to update the risk assessment and initiate new regulatory requirements, when appropriate, to ensure the protection of human health and the environment. Pesticides included in the registration review program are pesticides for which EPA completed a Re-registration Eligibility Decision under the FQPA.

This dicamba Tier II Incident and Epidemiology Report reviews human observation data from a variety of sources including:

- Human incident (poisoning) data from the following sources:
  - OPP's Incident Data System (IDS) database;
  - National Institute of Occupational Safety and Health (NIOSH) SENSOR-Pesticides;
  - National Pesticide Information Center (NPIC) (Agency Sponsored); and
  - California's Pesticide Incident Surveillance Program (PISP).
- Epidemiological studies from the open literature.

A Tier II incident and epidemiology report, as compared to a Tier I incident and epidemiology report, provides additional details and greater depth in scope of review of information relating to human exposure. Utilization of these data will aid HED in better defining and characterizing the potential risk of dicamba pesticide products to the U.S. population, and particular sub-groups such as workers and children.

Incident data are collected systematically, but differently, across the different databases used by the Agency with respect to such issues as coverage, certainty/confidence, fields/parameters reported, and usability. The three pesticide incident data sources (IDS, NIOSH SENSOR-Pesticides, and NPIC) were used in this dicamba report since they provide useful content and historical perspective. Various other comparable sources of data are available (e.g. the Bureau of Labor Statistics, emergency room outpatient surveillance, National Poison Data System (NPDS), etc.) but are not included in this review. By looking across the five data sources which were used, the Agency is confident that we are considering adequate and appropriate information to discern trends and patterns in permethrin-associated acute pesticide poisonings, or "incidents."

It is important to recognize, however, that reports of adverse health effects allegedly due to a specific pesticide exposure (i.e., an "incident") are largely self-reported and therefore, generally speaking, neither exposure to a pesticide nor reported symptoms (or the connection between the two) are validated. Therefore, only rarely can causation be determined or definitively identified based on incident data. However, incident information can provide important feedback to the Agency. Human incident data, in concert with other human observational studies (biomonitoring and epidemiological studies) and the human health risk assessment, can assist the Agency in determining potential risks of pesticides/pesticide product exposure, and can help characterize that risk. This review assesses acute pesticide poisoning incidents and published epidemiology studies to inform the preliminary risk assessment for dicamba.

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https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0187-0966

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2 REVIEW OF INCIDENT ANALYSIS

2.1 Incident Data System (IDS) (2015-2020)

OPP's IDS includes reports of alleged human health incidents from various sources, including mandatory Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Section 6(a)(2) reports from registrants, other federal and state health and environmental agencies, and individual consumers. Since 1992, OPP has compiled these reports in IDS. IDS contains reports from across the U.S. and most incidents have all relevant product information recorded. Reports submitted to the IDS represent anecdotal reports or allegations only, unless otherwise stated in the report.

IDS records incidents in one of two modules: Main IDS and Aggregate IDS:

- Main IDS generally contains incidents resulting in higher severity outcomes and provides more detail with regard to case specifics.[2] This system stores incident data for death, major and moderate incidents, and it includes information about the location, date and nature of the incident. Main IDS incidents involving only one pesticide are considered to provide more certain information about the potential effects of exposure from the pesticide.

- Aggregate IDS contains incidents resulting in less severe human incidents (minor, unknown, or no effects outcomes). These are reported by registrants only as counts in what are aggregate summaries.

For Main IDS from January 1, 2015 to July 31, 2020, there were 174 incidents reported that involved the active ingredient dicamba. Of these 174 incidents, seven incidents involved the single active ingredient dicamba (only). Six of these incidents were classified as moderate severity and one incident was classified as having no or unknown symptoms. These incidents are described in Appendix A, Table 1. The other 167 dicamba incidents reported involved multiple active ingredients. There was one death reported which was a suicide. In 2019 in Pennsylvania, a male ingested an entire bottle of the product. There were eight major severity incidents that are described in Appendix A, Table 2.

Thirty two incidents reported in from 2019 to July 31, 2020 were further analyzed for exposure scenarios and health effects. Four of these incidents were diagnosed by a health care professional as not being related to dicamba and not further reviewed. Of the remaining 28 dicamba incidents, most (n=13) individuals were homeowners that reported being exposed while applying the product. Other exposures include ingestion/suspected ingestion (n=5), contact with the product (n=3), drift (n=2), postapplication exposure (n=1), one occupational exposure to warehouse employees and three unknown exposures. The incident narratives can be found in Appendix A, Table 3. Individuals most often reported dermal symptoms, including rash, blisters and itchiness, followed by respiratory and neurological symptoms, including shortness of breath, respiratory irritation, confusion, dizziness, and headache. Other reported symptoms were cardiovascular, ocular and gastrointestinal symptoms which included eye irritation, chest pressure, vomiting and diarrhea.

For Aggregate IDS from January 1, 2015 to July 31, 2020, there were 1203 incidents reported involving dicamba. Twenty two incidents had no or unknown effects and 1181 incidents were classified as minor severity. Minor severity means that a person alleged or exhibited some symptoms, but they were minimally traumatic, the symptoms resolved rapidly and usually involved skin, eye, or respiratory

[2] Occasionally, low severity incidents are self-reported by the consumer directly to Main IDS.

irritation. Because these incidents fall within the categories reported as counts (which includes minor, unknown or no effects), there is no unique report that provides details about the incident.

2.2 SENSOR-Pesticides (2012-2017)

The Center for Disease Control's National Institute for Occupational Safety and Health (CDC/NIOSH) manages a pesticide surveillance program and database entitled the Sentinel Event Notification System for Occupational Risk (SENSOR)-Pesticides.[3] All cases must report at least two adverse health effects. Evidence for each case is evaluated for its causal relationship between exposure and illness based on the NIOSH case classification index.[4] Using standardized protocol and case definitions, SENSOR-Pesticides state coordinators, operating out of the state's department of health, receive state pesticide incident reports from local sources, then follow up with case sources to get incident scenario to obtain medical records and verify exposure scenario information.[5] This database includes pesticide illness case reports from multiple states from 1998-2017.[6]

A query of SENSOR-Pesticides from 2012-2017 identified a total of 130 cases involving dicamba. All cases involved exposure to multiple pesticide active ingredients, one of which was dicamba. Overall, the majority of cases were low in severity (86%). There were 17 cases that were moderate in severity and one case that was high in severity. Cases primarily involved homeowner applicator exposures.

The high severity incident report occurred in Washington in 2015 and was a residential exposure. The case resides about 100 feet away from an oat field that was being sprayed. She smelled the chemical coming into the cabin. She did not experience symptoms at that time; however, the next morning she woke up with a cough and a nosebleed. This case sought medical treatment seven days after her exposure; she reported sore throat, chronic cough, and runny nose. The case was diagnosed with an upper respiratory infection. The state's investigation found this exposure was due to spray drift from an application of a state-declared restricted-use pesticide (EPA Reg. # 71368-34).[7] The Washington State Department of Agriculture issued a Notice of Correction to the individual who made this application for "purchase and application of more than 1 gallon of a RUP without an applicator's license."

The majority of incidents involving dicamba were non-occupational (n=92) and primarily involved either homeowners applying a dicamba product (n=36) or a postapplication exposure of another member of the household to an application of dicamba at their residence (n=44).

For both non-occupational and occupational cases, there were many cases that accidentally sprayed themselves in the face and/or eyes while applying (n=42), or experienced a product spill or splash exposure scenario while they were using the pesticide. In most of the homeowner application cases, the individual was not wearing any PPE. This was true for many occupational cases as well. There were; however, some of the occupational cases that did wear PPE (including goggles, facemasks) but the protective gear was inadequate, for example, PPE was knocked off their face due to a high-pressure exposure incident. The following is a breakdown of exposure scenarios identified for the 130 dicamba cases:

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[3] SENSOR-Pesticides webpage: http://www.cdc.gov/niosh/topics/pesticides/overview.html.
[4] https://www.cdc.gov/niosh/topics/pesticides/pdfs/casedef.pdf
[5] https://www.cdc.gov/niosh/topics/pesticides/pdfs/pest-sevindexv6.pdf
[6] Currently participating states are: California, Florida, Illinois, Louisiana, Michigan, Nebraska, New Mexico, North Carolina, Oregon, Texas and Washington. The participating states for a given year vary depending on state and federal funding for pesticide surveillance.

[7] In addition to the federal restricted-use pesticide products, Washington Pesticide Laws and Related Regulations lists several state-designated restricted-use pesticides, including dicamba.

Application/handling-related exposures

- Equipment malfunctions, including hose breaks, pressurized pump bursts, leaking backpacks (n=14)
- Spill of product when mixing/loading/handling (n=12)
- Spray or splash to face when applying (n=12)
- Applying while windy (n=5)
- Touched face (n=3)
- General application exposures (n=26)

Post-application exposures

- Case was directly contacted/hit by an active application (n=11)
- Spray drift during an active application (n=9)
- Contact with residue when in a recently treated area (n=15)
- Other (non-contact residue) postapplication exposures when in a recently treated area (n=14)
- Accidental ingestion of product from a beverage container (n=3)
- Child found/tampered with product (n=3)
- Not specified (n=3)

Dicamba exposure routes were primarily dermal (n=70) or inhalation (n=58); followed by ocular (n=30) then oral/ingestion (n=14). Many cases reported multiple routes of exposure. The moderate and high severity cases (n=17) tended to involve inhalation exposures (n=10) and/or ocular (n=4); two more severe cases were oral exposures. The most frequently reported symptom among all cases was eye pain, burning or irritation (n=44). Reports of adverse health effects most often were neurological symptoms (n=59) including headache and dizziness; followed by dermal symptoms (n=52) including skin pain/irritation and redness; followed by respiratory symptoms (n=46) including upper respiratory pain/irritation; gastrointestinal symptoms (n=45) primarily nausea and vomiting; as well as ocular symptoms (n=44), primarily eye pain, burning, and/or irritation. Most cases were low in severity (86%) and resolved in less than three days.

While the product names and EPA registration numbers implicated in dicamba cases were numerous and varied, most product formulations were soluble concentrates or emulsifiable concentrates used to control weeds on lawns. Most of the dicamba product labels reviewed for this memo did require PPE, including protective eyewear, chemical resistant gloves, or chemical resistant aprons on the labeling. Homeowner applicators did not often report use of any PPE. All incidents reported exposure to multiple active ingredients including dicamba; other pesticide active ingredients frequently reported in the dicamba incidents include: 2,4-D, diquat dibromide, fluazifop-butyl, fluroxypyr, sulfentrazone, MCPA, and MCPP.

2.3 California's Pesticide Incident Surveillance Program (PISP) (2012-2017)

The Pesticide Illness Surveillance Program (PISP) maintains a database of pesticide-related illnesses and injuries. Case reports are received from physicians and via workers' compensation records. The local County Agricultural Commissioner investigates circumstances of exposure. Medical records and investigative findings are then evaluated by DPR technical experts and entered into an illness registry.

PISP contains both residential and occupational pesticide incidents. PISP has limited coverage (only California) and is therefore not useful for identifying national trends over time. However, the incident information is entered by professionals with expertise in pesticides who extensively follow-up on each reported case, establishing a high degree of confidence in the information provided for each reported incident.

In PISP from 2012-2017 there were 28 case reports involving dicamba. PISP evaluated the certainty of each case by reviewing the physical exposure and medical evidence and determined that 13 cases were probable, 11 cases were possible, and four cases were definite. Of these 28 cases, 23 cases were non-occupational exposures and five cases were occupational agricultural exposures. Overall, most cases (n=15) were applying the pesticide when they were exposed. Five cases were exposed from spray drift. See Table 1 to review all exposure scenarios among the 28 cases. See Appendix A, Table 4 to review the exposure details for all 28 dicamba incident reports identified in PISP.

Table 1. Exposure Type for Dicamba Incident Reports in CA PISP 2012-2017

Exposure Type	Case Count
Direct Spray/Squirt	6
Drift	5
Ingestion	4
Other	2
Spill/Other Direct	8
Unknown	3
Total	**28**

Twenty cases reported one or more dermal symptoms (n=20), followed by gastrointestinal symptoms (n=13) and ocular symptoms (n=11). Symptoms often reported among the PISP dicamba cases include skin irritation, rash, blisters, nausea, vomiting, burning and red/irritated eyes, and throat irritation.

2.4 National Pesticide Information Center (NPIC) (2015-2020)

The National Pesticide Information Center or NPIC is a cooperative effort between Oregon State University and EPA which is funded by EPA to serve as a source of objective, science-based pesticide information and to respond to inquiries from the public and to incidents. NPIC functions nationally during weekdays from 8:00 am to 12:00 pm Pacific Time through a toll-free telephone number in addition to the internet (www.npic.orst.edu) and email. Similar to Poison Control Centers, NPIC's primary purpose is not to collect incident data, but rather to provide information to inquirers on a wide range of pesticide topics, and direct callers for pesticide incident investigation and emergency treatment. Nevertheless, NPIC does collect information about incidents (approximately 4000 incidents per year) from the public and records that information in a database. While NPIC is a source of national incident information, it generally receives fewer reports than IDS. Regardless, if a high frequency is observed in IDS, NPIC provides an additional source of information to see whether there is evidence of consistency across national data sets or possibly duplication and additional information about the same incident(s).

From January 1, 2015 to May 14, 2020, 95 human incidents involving dicamba were reported to NPIC. NPIC estimates a certainty index that classifies an incident (including reported symptoms) as consistent or inconsistent with expected exposure to a pesticide, or whether the incident was unclassifiable. Of the 95

reported incidents, 26 were classified as consistent.[8] Of the 26 incidents that were classified as consistent, 18 incidents were classified as minor severity and eight incidents were classified as moderate severity. Of the remaining 69 incidents, 24 incidents were classified as inconsistent and/or unlikely related to dicamba exposure and 44 were asymptomatic and considered unclassifiable.

Half (n=13) of these incidents were due to exposure from drift, either from a neighbor's yard or a nearby agricultural field. Other exposures included spills and splashes (n=3), postapplication exposure (n=4) and homeowner applicator exposures (n=6). Individuals reported respiratory, neurological, dermal, ocular and gastrointestinal symptoms, including sore throat, coughing, difficulty breathing, rash, dizziness, tingling sensation, skin irritation, eye irritation stomach pain, and diarrhea.

2.5 Tier II Acute Incident Report Review Summary

Overall, the majority of dicamba incidents were low in severity (84% in IDS, 86% in SENSOR-Pesticides, NPIC 69%). IDS, SENSOR-Pesticides and PISP identified that most incidents involved homeowners exposed either when applying the product or through spills/splashes of the product. Most often these exposures were to lawncare products with more than one active ingredient. In addition, postapplication exposure to non-applying members of the household following application were reported. Among the occupational exposures to dicamba, these too primarily involved exposures while applying the pesticide, several of these involved application equipment failures; secondly several agricultural workers were directly hit with the pesticide spray during an active pesticide application. Across all four incident databases reviewed, there was a total 29 of spray drift-related exposures. Dicamba cases often reported adverse dermal, respiratory, and gastrointestinal health effects. Many cases also reported adverse gastrointestinal and ocular health effects.

3 TIER II EPIDEMIOLOGY REVIEW

3.1 Introduction

OPP conducted a systematic review of peer reviewed epidemiology studies that examined the association between dicamba and adverse health effects. The specific aims of the systematic review of the epidemiology literature were to:

1. Conduct a literature search and assemble a database of epidemiological studies examining the human health effects associated with dicamba exposure; and,
2. Review, summarize, and assess the quality of the assembled literature.

This report describes the systematic review approach and results of OPP's evaluation of epidemiology literature. This evaluation focused on characterizing results with respect to health outcomes evaluated in the literature and identifying strengths and limitations and overall quality of the study in the regulatory context.

3.2 Review Framework

The National Academy of Sciences National Research Council (NRC) and the National Academy of Medicine (formerly the Institute of Medicine) define systematic review as "a scientific investigation that

[8] Consistent means that the majority of reported symptoms are consistent with exposure to the active ingredient according to published information, and the time course between exposure, onset, and duration of symptoms could be conceivably consistent with the toxicology of the active ingredient and the reported exposure pathway is conceivably plausible based on the history provide

focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies. In a 2014 report, NRC identified systematic literature review strategies as "appropriate for EPA" and "specifically applicable to epidemiology and toxicity evaluations"[9] for regulatory purposes.

In 2016, EPA OPP published a framework for incorporating epidemiological data into risk assessments for pesticides which described a systematic review process relying on standard methods for collecting, evaluating, and integrating the scientific data supporting Agency decisions.[10] The epidemiology framework characterized "fit for purpose" systematic reviews for incorporating human epidemiology data into OPP risk assessments for pesticides, meaning that the complexity and scope of each systematic review is tailored to a specific analysis and follows the key characteristics outlined in the Cochrane Handbook:[11]

- Clearly stated set of objectives with pre-defined eligibility criteria for studies;
- Explicit, reproducible methodology;
- Systematic search to identify all relevant studies;
- Assessment of the validity of the findings from the identified studies; and,
- Systematic presentation and synthesis of the characteristics and findings of the included studies.

Following the procedures described in the OPP epidemiology framework, OPP conducted a formalized literature review to collect, evaluate, and integrate evidence from relevant epidemiological literature on the association between dicamba exposure and human health outcomes to evaluate whether exposure to this chemical is associated with an increased (or decreased) risk of adverse health outcomes.

3.3 Methods

3.3.1 Systematic Literature Search

The literature search methodology followed the guidance provided in the National Toxicology Program/Office of Health Assessment and Translation (NTP/OHAT) *Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration,* January 9, 2015. For the search, the following population, exposure, comparator, and outcome of interest (PECO) criteria below guided the inclusion/exclusion criteria and selection of terms:

3. **Population** of interest: Population studied must be humans with no restrictions, including no restrictions on age, life stage, sex, country of residence/origin, race/ethnicity, lifestyle, or occupation
4. Exposure: Exposure studied must be to dicamba in any application via any route of exposure.
5. Comparator: Exposed or case populations must be compared to a population with low/no exposure or to non-cases to arrive at a risk/effect size estimate of a health outcome associated with dicamba exposure.

[9] NRC. 2014. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: National Academies Press.
[10] US EPA. December 28, 2016. Office of Pesticide Programs' Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides. https://www3.epa.gov/pesticides/EPA-HQ-OPP-2008-0316-DRAFT-0075.pdf
[11] Higgins, J.P.T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M.J., and Welch, V.A. (Eds.) (2019). Cochrane Handbook for Systematic Reviews of Interventions. 2nd edition. Chichester (UK): John Wiley & Sons.

6. Outcome: All reported human health effects, with no restrictions on human system affected (effects could be based on survey or other self-report, medical records, biomarkers, publicly available health data, or measurements from human sample populations).

Based on these PECO criteria, inclusion/exclusion terms were identified, and a literature search was conducted in PubMed, PubMed Central, Science Direct, and Web of Science. The literature search included all peer-reviewed publications through January 2020. Results were limited to those with human subjects and an English language abstract. The search code used to identify publications is listed in **Table 2**.

Table 2. Dicamba Literature databases, search strategies, search dates, and publications returned

Database	Search Strategy	Search Date	Articles Returned
PubMed	((((“dicamba") AND (human AND ("adverse health effect*" OR epidemiologic stud* OR cohort* OR case control* OR case-control* OR cross section* OR cross-section* OR cluster* OR environmental exposure* OR occupational exposure* OR ecologic stud* OR aggregate stud* OR "pancreatic" OR “pancreas” OR "hematologic malignancy"))))	6/15/2020	35
PubMed Central	((((dicamba) AND (human AND ("adverse health effect*" OR epidemiologic stud* OR cohort OR case control* OR case-control* OR cross sectional OR cross-sectional OR cluster* OR environmental exposure* OR occupational exposure* OR ecologic stud* OR aggregate stud* OR "pancreatic" OR “pancreas” OR "hematologic malignancy"))))	6/16/2020	210
Science Direct	((“dicamba") AND (human AND ("adverse health effect" OR epidemiologic OR cohort OR case-control OR cross-sectional OR cancer OR "birth defect")))	10/13/2020	332

** indicates truncation (i.e., that alternate endings were searched)*

Based on the PECO criteria and search terms described above, the literature search aimed to identify original, peer-reviewed publications on epidemiologic studies. Exclusion criteria were also identified prior to collecting potentially relevant publications. Publications were excluded for the following reasons: not full text (*e.g.,* abstracts); not peer-reviewed; not in English; non-human study subjects; in-vitro studies; fate and transport studies; outcome other than human health effects (*e.g.,* environmental measures); experimental model system studies; no dicamba-specific investigation (*e.g.,* general insecticide); no risk/effect estimate reported (*e.g.,* case studies/series); and no original data (*e.g.,* review publications).[12] In addition, the review focused on epidemiology studies and excluded publications on acute poisonings and overexposure.

A key element of the inclusion/exclusion criteria hinged on the definition of “human health effect” outcomes. For the purposes of the epidemiology literature review, OPP considered human health effects via the toxicological paradigm presented by the NRC as pathologies or health impairments subsequent to altered structure/function.[13] Thus, studies with outcomes of altered structure (*e.g.,* DNA alteration, sister chromatid exchange, cell proliferation) or biomarker or other exposure outcomes (*e.g.,* in breast milk,

[12] While the search focused on original peer-reviewed publications, OPP does seek out and consider other sources of information that are not peer-reviewed (e.g. letters to the editor, corrections, commentary) on a case-by-case basis when this information provides clarification or other material findings or information of relevance to our evaluation of the literature.

[13] Goldstein, B., Gibson, J., Henderson, R., Hobbie, J., Landrigan, P., Mattison, D., Perera, F., Pfitzer, E., Silbergeld, E., Wogan, G. (1987). Biological markers in environmental health research. *Environmental Health Perspectives*, *7* (3-9).

urine, cord blood, or plasma) that did not also include an associated health pathology (*e.g.,* cancer, asthma, birthweight) failed to meet the inclusion criteria for "human health effects" for the purposes of this epidemiology literature review.

3.3.2 Supplemental Literature Search

To supplement the open literature search described above, OPP reviewed publications resulting from the Agricultural Health Study (AHS) for publications that satisfied the inclusion/exclusion criteria. The AHS is a federally funded study that evaluates associations between pesticide exposures and cancer and other health outcomes and represents a collaborative effort between the US National Cancer Institute (NCI), National Institute of Environmental Health Sciences (NIEHS), CDC's National Institute of Occupational Safety and Health (NIOSH), and the US EPA.

The AHS maintains on its website an electronic list of publications resulting from AHS studies using the AHS cohort.[14] These publications were imported into Endnote, and Endnote was used to run a full text search ("Any Field + PDF with Notes") for "dicamba" to ensure all AHS publications relevant to the epidemiology literature review were identified. AHS publications that satisfied the inclusion/exclusion criteria as described above were selected for inclusion in the epidemiology literature review.

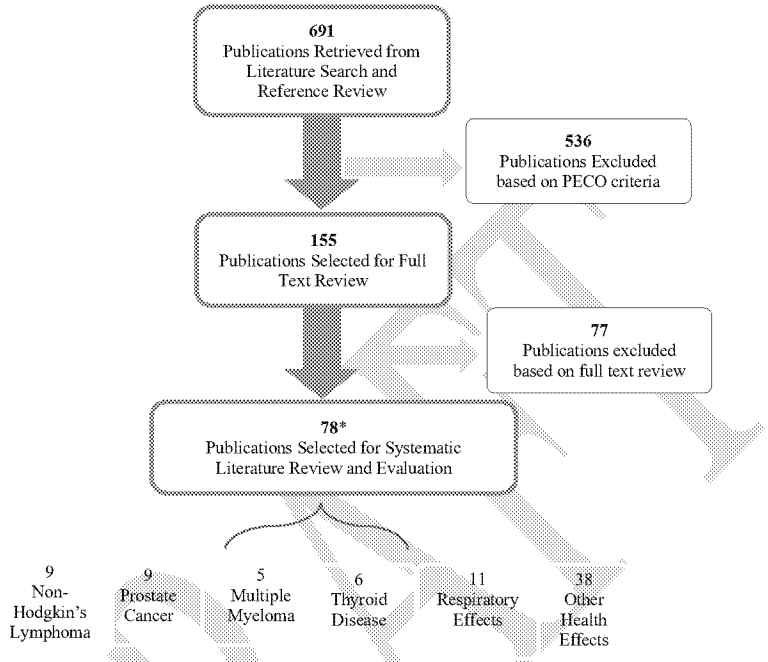
The final phase of data collection was a reference review of publications captured in the open literature search, the AHS publication search, and previously published OPP documents. References were examined to identify relevant publications that were not captured in either the open literature search or the AHS publication search. Resulting publications from this reference review that satisfied inclusion/exclusion criteria were selected for inclusion in the epidemiology literature review.

3.4 Literature Search Results

The search of the open literature returned 577 publications across PubMed, PubMed Central, and Science Direct and these publications were assembled into an EndNote Library (version x9) (15 duplicates and 62 AHS publications and were removed). Ten additional publications were retrieved through reference review. A total of 500 unique publications were retrieved from the open literature. The supplemental search of the AHS EndNote Database returned 104 publications that included the term "dicamba" in the text. A total of 604 publications (500 open literature + 104 AHS publications) underwent title and abstract screening for potential relevance using the PECO criteria and exclusion criteria described in the **Systematic Literature Search** section. Of these, 155 publications (51 open literature + 104 AHS publications) were selected for full text review based on this approach, and of these, 77 (28 open literature + 49 AHS publications) were excluded because they did not include dicamba-specific analysis. A total of 78 publications (23 open literature + 55 AHS publications) were selected for literature review and evaluation. A summary of the literature search and supplemental AHS search is provided in **Figure 1** below.

[14] Agricultural Health Study Publications: https://aghealth.nih.gov/news/publications.html

Figure 1. Summary of Literature Search Results



** Number of publications on health outcomes do not sum because some publications reported on multiple outcomes in a single publication.*

3.5 Literature Review and Evaluation Approach

3.5.1 Study Review and Quality Assessment

A total of 78 peer-reviewed epidemiologic publications were identified for OPP's literature review and evaluation. Each publication was reviewed and relevant information was summarized on study design, results, conclusions, the strengths and weaknesses of each study per the epidemiology framework (US EPA, 2016), and recount details including the exposure measurement, outcome ascertainment, number of participants (n), number exposed/number of cases, number in reference (un-exposed/control) group, effect measure (*e.g.,* odds ratio (OR), relative risk (RR), hazard ratio (HR), beta coefficient ((β)) and associated estimates of uncertainty and/or statistical significance (*e.g.,* confidence interval (CI), p-value), confounders considered, and methods of analysis. OPP considered these elements in assessing the quality of each publication and its applicability to an overall assessment of the health effects associated with dicamba exposure in terms of usefulness for regulatory purposes.

The assessment of study quality followed the OPP Framework. As shown in Error! Reference source not found.3, the study quality assessment for regulatory purposes considered aspects such as design, conduct, analysis, and interpretation of study results, including whether study publications incorporated a clearly articulated hypothesis; adequate assessment of exposure; critical health windows; valid and reliable outcome ascertainment; a sample representative of the target population; analysis of potential

confounders; characterization of potential systematic biases; evaluation and reporting of statistical power; and, use of appropriate statistical modeling techniques.

Table 3. Epidemiology Study Quality Considerations for Regulatory Purposes (Adapted from Table 2 in US EPA, 2016)

Parameter	High	Moderate	Low
Exposure assessment	Exposure assessment includes information on dicamba or metabolite in the body, quantitative air sample data, or high-quality questionnaire on chemical-specific exposure assessment during relevant exposure window	Questionnaire based individual level information on dicamba	Low quality questionnaire-based exposure assessment, or ecologic exposure assessment, with or without validation
Outcome Assessment	Standardized tool, validated in study population; or, medical record review with trained staff	Standardized tool, not validated in population, or screening tool; or, medical record review, methods unstated	Subject report, without additional validation
Confounder control	Good control for important confounders relevant to dicamba study question, and standard confounders	Moderately good control of confounders, standard variables, not all variables for dicamba study question	Multi-variable analysis not performed, no adjustments
Statistical Analysis	Appropriate to study question and design, supported by adequate sample size, maximizing use of data, reported well (not selective)	Acceptable methods, questionable study power (esp. sub-analyses), analytic choices that lose information, not reported clearly	Minimal attention to statistical analyses, comparisons not performed or described clearly
Risk of (other) bias (selection, differential misclassification, other)	Major sources of other potential biases not likely present, present but analyzed, unlikely to influence magnitude and direction of the risk estimate	Other sources of bias present, acknowledged but not addressed in study, may influence magnitude but not direction of estimate	Major study biases present, unacknowledged or unaddressed in study, cannot exclude other explanations for study finding

Note: Overall study quality ranking based on comprehensive assessment across the parameters.

Study design influenced the assessment of study quality. Cohort studies, which enable researchers to assess the temporality of exposure in relation to health outcome and to consider multiple health outcomes, were generally considered higher quality than other study designs. Case-control studies, which are susceptible to recall bias, were generally considered to be of lower quality than nested case-control studies, which may be less susceptible to selection and recall bias. Cross-sectional studies cannot distinguish temporality for exposure in relation to health outcomes; therefore, cross-sectional studies were generally considered lower quality than cohort or case-control studies and were regarded as hypothesis-generating in the absence of additional studies supporting an observed association. The lowest quality study design considered was ecologic, due to an inability to extrapolate observed associations from the group level to the individual level (ecological fallacy) inherent in the ecologic study design. Ecologic studies were generally regarded as hypothesis-generating studies (US EPA, 2016).

Studies that characterized the exposure-response relationship (*e.g.,* with a dose-response curve or trend statistic) were, in general, considered higher quality than studies that did not characterize exposure-response. Studies that specified temporality (*i.e.,* those that determined exposure preceded a health

outcome) and studies that specified and explored uncertainties in the analysis were, in general, considered higher quality than studies that failed to specify temporality and studies that lacked an examination of uncertainty. Consistent results between study groups (*e.g.,* a significant and positive association seen for both farmers and commercial applicator study groups within a single study) bolstered the assessment of study quality.

Risk estimates (estimates of effect) reported in epidemiological studies were generally considered as follows:

7. No evidence of a positive association between exposure and outcome (e.g., OR ≤ 1.00);
8. No evidence of a significant positive association (e.g., OR > 1.00 but not significant);
9. Evidence of a slight positive association (e.g., 1.00 < OR < 1.30 and significant);
10. Evidence of a positive association (e.g., 1.30 ≤ OR < 2.0 and significant);
11. Evidence of a moderately strong (e.g., 2.0 ≤ OR < 3.0 and significant) or strong (e.g., OR ≥ 3.0 and significant) positive association.[15]

However, we recognize that results that fail to attain statistical significance may still indicate clinical, biological, and/or public health importance and may warrant further exploration (US EPA, 2016). We particularly noted large observed associations (*e.g.,* OR ≥ ~2.5) even in the absence of significance, perhaps indicating a smaller than optimal sample size.

3.5.2 Categories of Evidence

The categories of evidence described in **Table 4** are guided by several documents that have been developed by EPA and others. These include as a main reference a document developed by the Institute of Medicine (now the Academies of Science, Engineering, and Medicine)[16] which detailed various "Categories of Association" which describes guidance for drawing conclusions regarding the overall strength of the evidence that exists regarding any putative linkage between an exposure and a health effect (IOM, 1998). Also considered in developing OPP's categories of evidence were the NTP's OHAT document on systematic review and evidence integration (Woodruff and Sutton, 2014), OPP's epidemiologic framework document (US EPA, 2016), and EPA's Preamble to the Integrated Science Assessments which serve as a scientific foundation for the review of EPA's National Ambient Air Quality Standards (US EPA, 2016).

In this memorandum, each category is assigned based on a case-by-case approach that considers the weight of the epidemiological evidence and expert judgement and not a binding or inflexible formulaic approach in deciding the number and/or quality of studies that would be necessary to assign a specific evidence category. When assigning a level of evidence category to an exposure and the body of evidence

[15] Although listed as OR (odds ratios) here, these characterizations are also applicable to risk ratios (RRs) and hazard ratios (HRs). For publications that reported ORs, RRs, and HRs, the confidence interval (CI) acted as a proxy for significance testing, with CIs that do not contain the null value (OR / RR / HR = 1.00) considered significant. P-value significance considered a critical value of $\alpha = 0.05$ unless otherwise specified by the authors and noted in the summaries here.

[16] IOM (1998). Veterans and Agent Orange Update 1998. National Academy Press. Washington, DC. https://www.nap.edu/read/6415/chapter/1. Some of this material is derived from and/or consistent with U.S. Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General.* Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004 and its Chapter 1 "Introduction and Approach to Causal Inference," available at: https://www.ncbi.nlm.nih.gov/books/NBK44695/. Much of this material is also presented in a more recent National Academies publication from 2018: National Academies of Sciences, Engineering, and Medicine 2018. *Gulf War and Health: Volume 11: Generational Health Effects of Serving in the Gulf War.* Washington, DC: The National Academies Press. https://doi.org/10.17226/25162.

pertaining to that health effect, the level of quality of the studies available in the peer-reviewed literature for that health effect, the strength of the associations (effect sizes) and consistency of the association in magnitude and direction across available studies was considered, as described in OPP's epidemiologic framework document.

Table 4. Tier II Epidemiology Studies Categories of Evidence

Evidence Category	Description
Sufficient Epidemiological Evidence of a Clear Associative or Causal Relationship	*Sufficient epidemiological evidence to suggest a clear associative or causal relationship between the exposure and the outcome.* There is high confidence in the available evidence to suggest that a clear associative or causal relationship exists between the exposure and the health outcome of interest. Studies are minimally influenced by chance, bias, and confounding. Further, additional epidemiological data, evidence, or investigations are unlikely to substantively affect the overall magnitude or direction of the observed association or result in a meaningful change with respect to any conclusions regarding this association. This level of evidence might be met, for example, if several high- or moderate- quality studies on different study populations, by different authors, in different settings, and/or using different epidemiological study designs that are likely to be minimally influenced by bias and confounding show a clear associative or causal relationship that is consistent among studies with respect to magnitude and direction of effect sizes. Such evidence is strengthened when one or more high- or moderate-quality studies also demonstrate dose-response trends with the range of these doses (exposures) considered sufficient to cover the range of expected human exposure levels (including the high end) and the evidence base consists of a least one high-quality prospective cohort study.
Limited but Insufficient Epidemiological Evidence of an Association	*Limited but insufficient epidemiological evidence to conclude that there is a clear associative or causal relationship between the exposure and the outcome.* There is some confidence that the available evidence accurately reflects a clear association between the exposure and the outcome, but the evidence is limited because the studies are of insufficient quantity, quality, (internal) validity, or consistency or because chance, bias, and confounding could not be ruled out with confidence. While the present body of evidence suggests that a relationship between exposure and disease outcome may possibly exist, additional high- or moderate-quality epidemiological data, evidence, or investigations could affect the overall magnitude or direction of the observed associations and might result in a meaningful change to this level of evidence category. This level of evidence category might be met, for example, if the body of evidence is: (1) based at least on one high-quality study suggesting a statistically significant relationship and the results of other high or moderate quality studies are mixed, contradictory, imprecise, ambiguous, or inconsistent; (2) based on several moderate-quality studies which show a relationship between exposure and outcome that is less pronounced than in (1); or (3) based on many studies (both moderate and possibly low-quality studies) showing a generally consistent direction and for which additional and more thorough analysis would be needed to make the determination of a relationship.

Evidence Category	Description
Insufficient Epidemiological Evidence of an Association	*Insufficient epidemiological evidence to conclude that there is a clear associative or causal relationship between the exposure and the outcome.* There is minimal confidence in the available evidence that the findings accurately reflect an association between the exposure and the outcome because the studies are of insufficient quantity, quality, (internal) validity, consistency, or statistical power to permit a conclusion to be reached, and/or chance, bias, or confounding may play an important role and cannot be ruled out. Further, additional high- or moderate-quality epidemiological data, evidence, or investigations could substantively affect the overall magnitude or direction of any observed associations. This level of evidence category might be met, for example, if the body of evidence is: (1) too small to permit conclusions, such as when there are no available studies to validate or corroborate the findings of a single moderate- or low-quality study; (2) based entirely on one or more studies judged to be of low-quality; or (3) based on multiple moderate- or low-quality studies, but the heterogeneity of exposures, outcomes, and methods leads to mixed, conflicting, imprecise, ambiguous, or contradictory conclusions.
No Epidemiological Evidence of an Association	*No epidemiological evidence to conclude that there is a clear associative or causal relationship between the exposure and the outcome.* There is no epidemiological evidence to suggest the presence of an association between an exposure and outcome. This level of evidence category might be met, for example, if the body of evidence consists of high- or moderate-quality studies that show no evidence of a statistically significant association and generally appear to have small effect sizes, and/or for which chance, bias, or confounding may play an important role.
Sufficient Evidence of No Causal Relationship	*Sufficient epidemiological evidence to suggest there is no causal relationship between the exposure and the outcome.* There is high confidence in the available evidence to suggest there is no causal relationship between the exposure and the outcome. The studies are minimally influenced by chance, bias, and confounding, and it is unlikely that additional epidemiological data, evidence, or investigations would meaningfully affect the current overall magnitude, direction, or conclusions about the association. This level of evidence category might be met, for example, if at least one high-quality study with adequate power (*e.g.*, ≥80%) to detect a meaningful effect size determined to be of substantive importance fails to show an effect and no other high or moderate quality studies provide affirmative evidence against this null result. In addition, data would also exist that suggests no significant dose-response trends are present with the range of these doses (exposures) considered sufficient to cover the range of expected human exposure levels (including the high end) and the evidence base consists of a least one high-quality prospective cohort study.

3.5.3 Background and Quality Considerations for the Agricultural Health Study

Many studies reviewed in this memorandum are part of the Agricultural Health Study (AHS). AHS is a federally funded effort begun in the early 1990s that evaluates associations between pesticide exposures and cancer and other health outcomes. The participant cohort includes more than 50,000 licensed private (farmer) and commercial pesticide applicators from Iowa and North Carolina in addition to their spouses (for a total of more than 90,000 participants). The AHS is a prospective cohort design in which enrollment occurred from 1993 - 1997; data collection is ongoing from both applicator and spousal participants. Because the AHS is a prospective cohort design, this means that much of the exposure information is collected *prior to* the diagnosis (or detection) of the disease, and this can potentially limit

to a substantial degree issues potentially related to (case) recall bias which can be a serious methodological weakness of many case-control studies. Such recall biases can be common among case-control designs where individuals that are either diseased (cases) or not (controls) are asked about their exposure histories. To the extent that cases and controls can differentially recall such exposures, such case-control designs can be subject to considerable biases. For the nested case-control studies within the AHS, this can potentially lead to recall biases depending on the degree to which either the study collects information from farmers (or next of kin) after the disease diagnosis and whether cases and controls are asked to provide supplemental information or more detailed questionnaires regarding exposure history or other practices. Cancer determination in the AHS is through cancer registries in the states of IA and NC and are considered reliable.

While the AHS generally provides high quality information with reliable data regarding pesticide usage and lifestyle factors and information on specific pesticides rather than simply pesticide classes or groups, collecting such exposure information can be complex and it can be difficult to judge its validity or reliability. The AHS has been reviewed in this regard and has been found to be generally reliable: the study design/questionnaire is particularly advantageous because it collects information on individual pesticides -- and not just groups or classes of pesticides as is characteristic of a number of other epidemiology studies. But individuals -- particularly over a number of years or decades – are exposed to a number and variety of pesticides which can complicate epidemiological analyses by introducing confounders or sometimes "collinearity" whereby it can be difficult to isolate causal or suggestive factors contributing to disease. In addition, field studies have shown wide variation in work and hygienic practices among farmers (and farm workers) and exposures – especially exposures over long time periods time – and can thus be difficult to accurately assess. The AHS does have in place an algorithm that attempts to account for certain work or hygienic practices by adjusting estimated exposures to account for use by farmers of personal protective equipment and practices; this algorithm considered such work and hygienic practices, including the mix of activities performed (*e.g.*, mixing/loading vs. application) and provides exposure estimates on both a cumulated (lifetime day)- and intensity-weighted cumulated (intensity-weighted lifetime day)- basis. Nevertheless, the AHS algorithms assume that total (cumulated) lifetime exposure depends on the multiplicative product of annual frequency of applications by a farmer and the associated number of years of application and this may not be strictly true and could systematically overestimate or underestimate exposures. Too, use practices such as application equipment and methods for a given pesticide can change over time, in addition to formulations (and farming practices in general) which can add additional uncertainties with respect to any assessment of cumulated exposure.

3.6 Literature Review and Evaluation

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This section presents a review and evaluation of the epidemiologic literature on the potential association between dicamba exposure and carcinogenic and non-carcinogenic adverse health outcomes. The review and evaluation of the available literature is organized by carcinogenic and non-carcinogenic adverse health outcomes. For each of the health outcome sections, individual study publications are summarized and then an overall evaluation of findings is characterized. **Appendix B** provides a tabular summary of all the studies reviewed, with respect to their design, methods, results, and study quality organized by health outcome.

3.6.1 Carcinogenic Health Outcomes

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For carcinogenic health outcomes, EPA conducted a review of 33 publications that investigated the relationship between dicamba exposure and 27 carcinogenic effects including: all cancers combined, bladder cancer, brain cancer, breast cancer, cancers of the large intestines, esophageal cancer, laryngeal cancer, lip cancer, liver and intrahepatic bile duct cancers, lung cancer, lymphohematopoietic cancers,

melanoma, pancreatic cancer, prostate cancer, cancer of the small intestine, soft tissue sarcoma, stomach cancer, testicular cancer, tongue cancer and tonsil cancer. These 33 studies for these health outcomes are described below.

Cancer (all sites)

Three publications (Flower et al., 2004; Samanic et al., 2006; Lerro et al., 2020) evaluated the relationship between dicamba exposure and all cancers in adults and in children.

- Flower et al. (2004), investigated the risk associated with dicamba exposure and childhood cancer (any cancer) as a result of previous parental occupational exposures to pesticides including dicamba using data from the AHS. Parents participating in the AHS were identified via enrollment questionnaires (1993-1997), and cases were defined as children of AHS study participants in Iowa, who were born in 1975 or after, and were diagnosed with cancer according to the Surveillance, Epidemiology, and End Results (SEER) childhood cancer classification at the age of ≤ 19 years.[17] Childhood cancer cases were determined both retrospectively and prospectively following their parent's enrollment within the AHS (1993-1997), and each case was ascertained using birth certificates and linkage to the state cancer registry. A self-reported questionnaire detailing pesticide usage during study enrollment was completed by AHS farmers and their wives, including the application and mixing of 50 specific pesticides. Logistic regression was used to calculate ORs and 95% CIs for dicamba ever exposure and all childhood cancers, adjusted for child's age at enrollment. Of the 17,280 children included in the analysis, 4,942 (29%) were exposed to dicamba through parental (mother and/or father) dicamba ever use while pregnant. Of the total 50 childhood cancer cases identified in the study, nine cases reported parental dicamba exposure and subsequent childhood cancer in their offspring. No evidence of a positive association was observed between parental dicamba exposure and childhood cancer among a very small (n ≤ 10) number of cases (OR = 0.69; 95% CI: 0.32, 1.48; n = 9 exposed cases).

  The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths included the study design, the ascertainment of cases using the cancer registry and birth certificate data, and the retrospective and prospective means used to identify cases. A main limitation of the study included the indirect exposure measurement (parental self-reported dicamba use). Study authors reported that exposure did precede all childhood cancer cases, however the time frame between parental self-reported dicamba exposure and duration of use extended up to ten years, making it difficult to identify the true window of dicamba exposure – e.g., prior to conception or prior to the birth of the child.

- Samanic et al. (2006) examined the association between dicamba exposure and several cancers, including all cancers among pesticide applicators in the AHS prospective cohort. The study population included male pesticide applicators living in Iowa and North Carolina who completed the AHS enrollment questionnaires and had complete data on dicamba and covariates. Cases of incident cancer (first primary cancer) diagnosed between enrollment (1993 - 1997) and December 31, 2002 were identified via linkage to state cancer registries. Those who reported cancer at the time of enrollment (n = 1,075) or were missing information about dicamba (n = 6,362); or missing information about covariates (n = 6,608) were excluded from the analysis. Females were excluded from the analysis because there were only four cancer cases among female participants. Pesticide exposure was assessed using responses about pesticide exposure captured on the enrollment questionnaires. Poisson regression was used to estimate individual RRs and 95% CIs, for the

Commented [JE5]: There are two publications on childhood cancer – Flower et al. 2004 examined all childhood cancers and Metayer et al., which examined Acute Lymphoblastic Leukemia.

Lerro et al., also examines Acute Lymphoblastic Leukemia in adults in the AHS.

Because of this, I removed the Childhood Cancer Section –and put Flower et al. 2014 under All Cancers and Metayer under Leukemias

[17] Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, et al., eds. 1999. Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975–1995. Bethesda, MD: National Cancer Institute, SEER Program.

association between dicamba exposure and several cancers, adjusting for age, education, state of residence, smoking (pack years), family history of cancer, and total lifetime days of pesticide application. Lifetime exposure days were grouped into tertiles on the basis of the distribution among all cancer cases combined and the highest tertile was divided at the median to create the following categories for lifetime exposure days for all cancer types: No exposure, 1 to < 20 days, 20 to < 56 days, 56 to < 116 days, and ≥ 116 days. For the intensity-weighted lifetime exposure days analysis, categories of exposure included no exposure, 1 to < 86.6, 86.6 to < 344.3, 344.3 to < 739.2, and ≥ 739.2 intensity-weighted days. Among the 41,969 male pesticide applicators included in the analysis, 22,036 (52.5%) reported exposure to dicamba. Of the 1,694 cancer cases included in the analysis, 807 reported exposure to dicamba. No evidence of a significant positive association was reported for lifetime days of dicamba exposure at all exposure levels and all cancers with the no exposed group and the low exposure group as the referent (0.90 < all RRs < 1.18; all 95% CIs encompassed the null value of 1.0; with n = 157 - 254 exposed cases per exposure category; all p-trends > 0.05). Similarly, no evidence of a significant positive association was reported for all exposure categories of intensity-weighted lifetime exposure days of dicamba and all cancers with the no exposed group and the low exposure group as the referent (0.90 < all RRs < 1.15; all 95% CIs encompassed the null value of 1.0; with n = 131 - 278 exposed cases per exposure category; all p-trends > 0.05).

The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The ranking was based on the general strengths of the AHS, including its prospective design, ability to identify cancer cases through linkage to cancer registries, and exposure assessment approach which examined cumulative lifetime exposure to dicamba. Limitations were noted including the fact that the authors did not correct for/adjust for multiple comparison/multiple testing and that we would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported.

- Lerro et al. (2020) investigated the association between dicamba exposure and several cancers including all cancers combined using data from the AHS prospective cohort. The study population (n = 49,992) consisted of pesticide applicators living in Iowa and North Carolina who were enrolled in the AHS cohort and who reported information on dicamba exposure at enrollment and follow-up. Incident cancer cases were identified using Iowa and North Carolina state cancer registry files from enrollment (1993-1997) through December 2014 in North Carolina and December 2015 in Iowa. International Classification of Diseases for Oncology (ICD-0-2) codes were used to classify cancer sites. Dicamba exposure was assessed through the enrollment questionnaire (1993 – 1997) and the first follow-up interview five years after enrollment (1999 – 2005). Multiple imputation was used to estimate pesticide exposures at follow-up for individuals who did not complete the interview (n = 20, 968, 37%). Poisson regression was used to calculate relative risks and 95% confidence intervals for each category of intensity-weighted days of dicamba use compared with no use, adjusting for age, race, sex, smoking, state, applicator type, education, imazethapyr use (Spearmen p = 0.49), and family history of cancer. The analysis for all cancers was also adjusted for pack-years smoked. Cumulative intensity-weighted days were categorized as no exposure or quartiles of intensity-weighted days of exposure among all incident cancer cases for sites with >20 exposed (no use, 5.0 – 449.5 days, 449.6 – 1260.0 days, 1260.1 – 3,698 days, >3,689 days) or based on the median, as no, low or high exposure for cancers and subtypes with 10–20 exposed cases (no use, 5.0 – 1,260.0 days, > 1,260.0 days). Among the 49,922 applicators, 26,412 (52.9%) reported dicamba exposure and among the 7,491 all cancer cases combined, 3,770 reported dicamba exposure. No evidence of a significant positive association was reported for any exposure category of dicamba intensity-weighted lifetime days of exposure and all cancers among pesticide applicators in the AHS (0.93 < RR < 1.01; all 95% CIs encompassed the null value of 1.0; with n = 941 – 944 exposed cases per exposure category), with the no exposure group as the referent.

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The general strengths of the publication included the underlying prospective design of AHS, focus on U.S. agricultural populations, and availability of a U.S. registry to comprehensively identify cancer cases. Lerro et al. (2020) indirectly assessed dicamba exposure based on the AHS survey instrument. Limitations were noted including the fact that the authors did not correct for/adjust for multiple comparison/multiple testing and that we would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported. We note also that

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and all cancers among adults and children. This determination is based on a limited body of evidence that consisted of one case-control study on children and two cohort studies on adults that were rated moderate quality. Flower et al. (2004), leveraged the AHS cohort to examine the association between parental exposure to dicamba and childhood cancer and reported no evidence of a positive association, among a very small number ($n < 10$) of potentially exposed cases based on paternal self-report of dicamba use. As such, the effect estimate was relatively imprecise and based on an indirect exposure assessment approach that may not fully reflect the exposure experience by children. In addition to the small number of cases with indirect dicamba exposure, the study was unable to assess direct dicamba exposure among the children; instead, the study relied on father's (pesticide applicator's) self-reported dicamba use. Furthermore, for the father's self-reported exposure, the time frame of pesticide exposure and duration of use extended up to ten years, making it difficult to identify the specific window of time when exposure to specific pesticides actually occurred – e.g., prior to conception or prior to the birth of the child. However, the study authors reported that exposure did precede all childhood cancer cases. Finally, the very small number of exposed cases ($n = 9$) severely restricts the ability to interpret with confidence the observed odds ratio.

Two additional AHS studies, (Samanic et al., 2006; Lerro et al., 2020), investigated the relationship between dicamba exposure and all cancers among adult pesticide applicators enrolled in the AHS prospective cohort and both reported no evidence of a significant positive association between dicamba exposure and all cancers. Several strengths were noted in both studies including the prospective cohort study design as part of the AHS and the ascertainment of cancer using established cancer registries. The study quality of both studies was moderate as both studies did not correct for multiple comparisons and we would expect several statistically significant results to go away after such statistical adjustment.

Bladder cancer

Three publications (Samanic et al., 2006; Koutros et al., 2016; Lerro et al., 2020) examined the association between dicamba exposure and bladder cancer. Results from Lerro et al. (2020) for bladder cancer all: i) were not statistically significant; ii) had RRs < 1.5; and, iii) displayed no trends, and were thus reported separately in **Appendix C**.

- Samanic et al. (2006) examined the association between dicamba exposure and several cancers, including bladder cancer among pesticide applicators in the AHS prospective cohort. The study population included male pesticide applicators living in Iowa and North Carolina who completed the AHS enrollment questionnaires and had complete data on dicamba and covariates. Cases of incident cancer (first primary cancer) diagnosed between enrollment (1993 - 1997) and December 31, 2002 were identified via linkage to state cancer registries. Those who reported cancer at the time of enrollment ($n = 1,075$) or were missing information about dicamba ($n = 6,362$); or missing

information about covariates (n = 6,608) were excluded from the analysis. Females were excluded from the analysis because there were only four cancer cases among female participants. Pesticide exposure was assessed using responses about pesticide exposure captured on the enrollment questionnaires. Poisson regression was used to estimate individual RRs and 95% CIs, for the association between dicamba exposure and several cancers, adjusting for age, education, state of residence, smoking (pack years), family history of cancer, and total lifetime days of pesticide application. Lifetime exposure days were grouped into tertiles on the basis of the distribution among all cancer cases combined and the highest tertile was divided at the median to create the following categories for lifetime exposure days for all cancer types: No exposure, 1 to < 20 days, 20 to < 56 days, 56 to < 116 days, and ≥ 116 days. For the intensity-weighted lifetime exposure days analysis, categories of exposure included no exposure, 1 to < 86.6, 86.6 to < 344.3, 344.3 to < 739.2, and ≥ 739.2 intensity-weighted days. Among the 41,969 male pesticide applicators included in the analysis, 22,036 (52.5%) reported exposure to dicamba. Of the 72 bladder cancer cases included in the analysis, 29 reported exposure to dicamba. No evidence of a positive association was reported for any exposure level of lifetime days of dicamba use and intensity-weighted lifetime days of dicamba use with the no exposed group as the referent (0.46 < all RRs < 0.89; all 95% CIs encompassed the null value of 1.0; with n = 4 - 13 cases per exposure category; all p-trends > 0.05). For the lifetime days analysis with the low exposed group as the referent, no evidence of a significant positive association was reported (1.11 < all RRs < 1.39; all 95% CIs encompassed the null value of 1.0; with n = 6 - 9 cases per exposure category; all p-trend > 0.05). For intensity-weighted lifetime days of dicamba use, with the low exposure group as the referent, evidence of a positive association was reported in the middle exposure group with the low exposure group as the referent among a very small number of cases (*344.25 - < 739.2 days* – RR = 1.70; 95% CI: 1.548, 5.27; with n = 6 exposed cases). No evidence of a significant positive association was reported for the other two exposure categories of intensity-weighted lifetime exposure days with the low exposure group as the referent (0.94 < all RRs < 1.95; all 95% CIs encompassed the null value of 1.0; with n = 4 - 13 cases per exposure category; all p-trends > 0.05).

The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The ranking was based on the general strengths of the AHS, including its prospective design, ability to identify cancer cases through linkage to cancer registries, and exposure assessment approach which examined cumulative lifetime exposure to dicamba. Limitations were noted including the fact that the authors did not correct for/adjust for multiple comparison/multiple testing and that we would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported. We note the very small sample size.

- Koutros et al. (2016) investigated the association between pesticides, including dicamba, and bladder cancer incidence among study participants in the prospective AHS cohort. The study population included male pesticide applicators in Iowa and North Carolina, with incident bladder cancer cases identified through cancer registry files in Iowa and North Carolina through 2011. Pesticide exposure was assessed via two self-administered questionnaires, one administered during study enrollment and a second follow-up questionnaire administered five years after enrollment. Investigators used this questionnaire data to estimate intensity-weighed lifetime days of use, with exposure category cut-points at 227.5, 760.25, 2,016, and 6,734.67 days of dicamba use. Poisson regression was used to calculate RRs, adjusting for age, race, state of residence, pack-years of cigarettes, and pipe smoking. Among the study population (n = 54,344), 321 bladder cancer cases were reported, and 125 cases reported exposure to dicamba. No evidence of a positive association was reported between dicamba exposure and bladder cancer (RR = 0.84; 95% CI: 0.62, 1.14) based on ever/never use. For the intensity-weighted lifetime days of exposure analysis, no evidence of a positive association was reported between dicamba exposure and bladder cancer in any exposure category (0.70 ≤ all RRs ≤

0.92; all 95% CIs encompassed the null value of 1.0; with n = 31 - 32 cases per exposure category; p-trend > 0.05).

In additional analyses of intensity-weighted lifetime days of dicamba use stratified by smoking status (never, former, and current smoker strata), no evidence of a significant positive association was reported between any exposure category of dicamba exposure and bladder cancer risk among never, former, and current smokers ($0.23 \leq RR \leq 1.14$; all 95% CIs encompassed the null value of 1.0; with n = 2 - 20 exposed cases, p-trends ≥ 0.05). Evidence of a significant negative association was reported between the highest exposure category of current smokers and bladder cancer and was based on a very small number of exposed cases (RR = 0.23; 95% CI: 0.05, 0.98; with n = 2 exposed cases; p-trend = 0.05) and an inverse exposure-response trend was reported for current smokers. Likelihood ratio tests to assess the differences between the never, former smoking strata found no evidence of effect modification by smoking on the relationship between dicamba exposure and bladder cancer (p-interaction > 0.05).

The overall quality of the study was ranked high based on the study quality criteria provided in the OPP Framework. The ranking was based on the general strengths of the AHS, including the prospective study design, ability to identify cancer cases through linkage to cancer registries, and the pesticide exposure assessment.

- Lerro et al. (2020) investigated the association between dicamba exposure and several cancers including bladder cancer using data from the AHS prospective cohort. The study population (n = 49,992) consisted of pesticide applicators living in Iowa and North Carolina who were enrolled in the AHS cohort and who reported information on dicamba exposure at enrollment and follow-up and is described in greater detail in the Cancer (all sites) section above. Briefly, incident cancer cases were identified from enrollment (1993-1997) through December 2015 and dicamba exposure was assessed through the enrollment and 5-year follow-up interview questionnaires. Poisson regression was used to calculate relative risks and 95% confidence intervals for each category of intensity-weighted days of dicamba use compared with no use, adjusting for age, race, sex, smoking, state, applicator type, education, imazethapyr use (Spearmen p = 0.49), and family history of cancer. Among the 49,922 applicators, 26,412 (52.9%) reported dicamba exposure and among the 374 bladder cancer cases, 191 reported dicamba exposure. No evidence of a significant positive association was reported for any exposure category of dicamba intensity-weighted lifetime days of exposure and bladder cancer among pesticide applicators in the AHS ($0.77 < RR < 1.16$; all 95% CIs encompassed the null value of 1.0; with n = 40 – 54 exposed cases per exposure category), with the no exposure group as the referent.

  The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The general strengths the prospective design of AHS, focus on U.S. agricultural populations, and availability of a U.S. registry to comprehensively identify cancer cases and the exposure assessment. We note that authors did not correct for/adjust for multiple comparison/multiple testing and we would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and bladder cancer. This determination was based on three publications (Samanic et al., 2006; Koutros et al., 2016; Lerro et al., 2020) that investigated the potential association among the AHS pesticide applicators. Samanic et al. (2006) reported

evidence of a positive association in the middle exposure category of intensity-weighted lifetime days of dicamba use with the low exposure group as the referent among a very small number of cases. And, no evidence of a significant positive association between dicamba exposure and bladder cancer in any exposure category of intensity-weighted lifetime exposure days and lifetime exposure days with the no exposed group. The quality of the study was ranked moderate. Lerro et al. (2020), reported no evidence of a significant positive association for any intensity-weighted lifetime days of dicamba exposure category and bladder cancer with the no exposure group as the referent among pesticide applicators in the AHS with longer follow-up time and more cases. Both Samanic et al. (2006) and Lerro et al. (2020) were ranked moderate study quality and multiple comparisons without adjustment for multiple comparisons was considered a limitation. The third publication, Koutros et al. (2016), reported no evidence of a positive association between dicamba exposure and bladder cancer among AHS pesticide applicators based on ever/never use. Further analyses that considered intensity-weighted lifetime days of dicamba use and intensity-weighted lifetime days of dicamba use stratified by smoking status (never, former, and current smoker strata), reported no evidence of a significant positive association between dicamba exposure and bladder cancer, with no evidence of statistically significant p-trends. The quality of the study was ranked high.

Brain and Spinal Cancer (Glioma)

Three studies (Lee et al., 2005, Yiin et al., 2012; Lerro et al., 2020) evaluated the association between dicamba exposure and glioma

- Lee et al. (2005) investigated the association between farming and agricultural pesticide use, including dicamba, and glioma in the Nebraska Health Study II, a case-control study of adults in eastern Nebraska. The study population included white residents of eastern Nebraska, ≥21 years old. Cases of incident primary glioma diagnosed between July 1st, 1988 and June 30th 1993 with histological confirmation were identified using the Nebraska Cancer Registry and participating hospitals in Lincoln and Omaha. Controls for the current study were randomly selected from the control group of a previous study covering the same base population and were frequency matched by age, sex, and vital status to the combined distribution of the glioma, stomach, and esophageal cancer cases. Demographic, medical and family history, occupational, and, pesticide exposure information (for those who lived or worked on farm) was collected via telephone interview conducted during 1992-1994. Pesticide exposure information was limited to use prior to 1985, the time period of the previous study. Interviews were conducted for 251 cases and 498 controls; however most interviews were conducted via proxy (76% of cases, 60% of controls) who were primarily spouses (45%) or other primary relatives (46%). Unconditional logistic regression was used to calculate ORs and 95% CIs for farming activity and for individual pesticide use, adjusted for age, respondent type, and sex, with the non-farmers as a reference group. Among the 251 cases and 498 controls included in the final analysis, 11 cases and 26 controls reported dicamba exposure. No evidence of a significant positive association was reported for dicamba ever use and glioma among farmers in Nebraska (OR = 1.20; 0.50, 2.70; with n = 11 exposed cases). When stratified by type of respondent, no evidence of a significant positive association was reported between dicamba ever use and glioma among those cases who had a proxy respondent (OR= 2.00; 95% CI: 0.70, 5.70; with n = 8 exposed cases and n = 13 exposed controls). No evidence of a positive association was reported among cases who completed the interview themselves (OR = 0.50; 95% CI: 0.10, 1.90; with n = 3 exposed cases and n = 13 exposed controls).

  The quality of the study was ranked low quality based on the study quality criteria provided in the OPP framework. The study had several important limitations related to its design, exposure assessment approach, statistical analysis, and ability to control for confounding. With regard to study

design, Lee et al. (2005) used a case-control approach and may have introduced selection bias when recruiting their control group. Differences between the results for the self-reporting respondents and the proxy respondents illustrate the possible problem, as the control groups for each of these respondents were constructed differently and each could be biased in a different way. In the analysis, the reference group for the statistical tests was non-farmers, even though the pesticide use questions were not asked of non-farmers. As a result, the results for pesticides are confounded with farmer versus non-farmers and control groups with different proportions of farmers will result in different statistical results. The use of respondent-reported dicamba use to ascertain exposure introduced further uncertainty because it is not possible to attribute the increased odds of glioma to dicamba exposure alone. In particular, the self-reporting and proxy respondents have different levels of knowledge about pesticide use and possibly different motives for responding. Moreover, self-reported exposure assessment is likely to be subject to differential misclassification because study participants may incorrectly recall previous pesticide usage. In addition to these limitations, we note the small number of exposed cases restricts the ability to interpret with confidence the reported odds ratios.

- Yinn et al. (2012) investigated the association between pesticides, including dicamba, and glioma among rural pesticide applicators enrolled in the Upper Midwest Health Study (UMHS) a population-based case-control study. The study population included participants residing in four states (Michigan, Iowa, Wisconsin, and Minnesota), aged 18 – 80 (between ascertainment/diagnosis in 1995 through January 1997). Cases of histologically confirmed glioma were identified via participating medical facilities, oncologists, and neurosurgeons in the area, and state cancer registry was checked to capture any missed diagnoses. Controls included participants aged 18 – 80 years old, with or without a self-reported history of cancer other than glioma who were randomly selected from state driver's license/nondriver ID records and from Health Care Financing Administrations Medicare data within 10 year age group as determined by the age distribution of glioma cases in that state from 1992 – 1994. Controls were frequency matched to cases by state. Pesticide exposure (cumulative use and lifetime intensity weighted) through 1992 was assessed using information collected on an interviewer-administered questionnaire. Demographic information and occupational and medical histories were also collected via the questionnaire. Unconditional logistic regression was used to estimate ORs and 95% CIs for the association between cumulative years and estimated lifetime cumulative exposure of farm pesticide use and glioma; adjusted for 10-year age group, sex, age, and education (less than high school, high school graduate, college graduate). Proxy respondents were used in this study in the event the cases were deceased or impaired and unable to participate in the study. A separate analysis was conducted with and without proxy respondents, in an effort to examine any differences that may exist. Among the 778 and 1,175 total cases and controls, 228 (29%) glioma cases and 417 (35%) controls reported exposure to pesticides while being on a farm. A further analysis within this study then looked at the relationship between pesticide exposure including dicamba among study participants whose occupation was <u>not</u> farm-related. Of the total 65 cases and 34 controls who reported pesticide exposure in <u>non-farm</u> jobs, 4 cases and 10 controls reported dicamba exposure among the sample population that included proxy respondents. No evidence of a positive association was reported for dicamba exposure and glioma among non-farm applicators (OR = 0.55; 95% CI: 0.17, 1.79; with n = 4 exposed cases and n = 32 exposed controls). Similarly, no evidence of a positive association was reported between dicamba exposure in non-farm jobs and glioma among non-farm applicators, *when proxy respondents were excluded* (OR = 0.81; 95% CI: 0.21, 3.10; with n = 3 exposed cases and n = 10 exposed controls). An additional analysis evaluated pesticide use among cases who reported home and garden pesticide usage. A total of 399 cases with proxy respondents and 204 cases without proxy respondents reported pesticide exposure throughout the home and through gardening, and no evidence of a positive association was reported between dicamba exposure and glioma in either analysis (*Proxy respondents included* - OR = 0.76; 95% CI:

0.47, 1.24 with n = 27 exposed cases; *Proxy respondents excluded* – OR = 0.87; 95% CI: 0.48, 1.58 with n = 16 exposed cases).

The quality of the study was ranked moderate quality based on the study quality criteria provided in the OPP framework. The study had several important limitations related to its design, exposure assessment approach, statistical analysis, and ability to control for confounding. With regard to study design, Yinn et al. (2012) used a case-control approach and may have introduced selection bias when recruiting their control group. A limitation of the study is the large number of proxy respondents used to complete interviews for the cases (45% of case interviews), relative to the controls (3% of control interviews). Although the study authors mentioned they tried offsetting the number of proxies used by conducting two separate analyses (with and with proxy respondents), inaccurate information obtained from the proxy respondents was still a strong possibility, potentially interfering with estimates of some of the observed outcomes. The use of respondent-reported dicamba use to ascertain exposure introduced further uncertainty because it is not possible to attribute the increased odds of glioma to dicamba exposure alone. In particular, the self-reporting and proxy respondents have different levels of knowledge about pesticide use and possibly different motives for responding. Moreover, self-reported exposure assessment is likely to be subject to differential misclassification because study participants may incorrectly recall previous pesticide usage. In addition to these limitations, findings on dicamba are based on only a small number of exposed cases and do not provide reliable effect estimates.

- Lerro et al. (2020) investigated the association between dicamba exposure and several cancers including brain cancer using data from the AHS prospective cohort. The study population (n = 49,992) consisted of pesticide applicators living in Iowa and North Carolina who were enrolled in the AHS cohort and who reported information on dicamba exposure at enrollment and follow-up. Incident cancer cases were identified using Iowa and North Carolina state cancer registry files from enrollment (1993-1997) through December 2014 in North Carolina and December 2015 in Iowa. International Classification of Diseases for Oncology (ICD-0-2) codes were used to classify cancer sites. Dicamba exposure was assessed through the enrollment questionnaire (1993 – 1997) and the first follow-up interview five years after enrollment (1999 – 2005). Multiple imputation was used to estimate pesticide exposures at follow-up for individuals who did not complete the interview (n = 20, 968, 37%). Poisson regression was used to calculate relative risks and 95% confidence intervals for each category of intensity-weighted days of dicamba use compared with no use, adjusting for age, race, sex, smoking, state, applicator type, education, imazethapyr use (Spearmen p = 0.49), and family history of cancer. Cumulative intensity-weighted days were categorized as no exposure or quartiles of intensity-weighted days of exposure among all incident cancer cases for sites with > 20 exposed (no use, 5.0 – 449.5 days, 449.6 – 1260.0 days, 1260.1 – 3,698 days, >3,689 days) or based on the median, as no, low or high exposure for cancers and subtypes with 10–20 exposed cases (no use, 5.0 – 1,260.0 days, > 1,260.0 days). Among the 49,922 applicators, 26,412 (52.9%) reported dicamba exposure and among the 85 brain cancer cases, 48 reported dicamba exposure. No evidence of a significant positive association was reported for any exposure category of dicamba intensity-weighted lifetime days of exposure and brain cancer among pesticide applicators in the AHS (0.88 < RR < 1.23; all 95% CIs encompassed the null value of 1.0; with n = 10 – 15 exposed cases per exposure category; p-trend = 0.81), with the no exposure group as the referent.

  The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The general strengths of the publication included the underlying prospective design of AHS, focus on U.S. agricultural populations, and availability of a U.S. registry to comprehensively identify cancer cases. Lerro et al. (2020) indirectly assessed dicamba exposure based on the AHS survey instrument. Limitations were noted including the fact that the authors did

not correct for/adjust for multiple comparison/multiple testing and that we would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported.

EPA Conclusion

Overall, there is *insufficient epidemiological* evidence at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and brain cancer including glioma. Three publications were identified that assessed the association between dicamba exposure and brain cancer (Lee et al., 2005, Yiin et al., 2012; Lerro et al., 2020). Lee et al. (2005) reported no evidence of a positive association between dicamba exposure and glioma in a case-control study in Nebraska. Proxy respondents were used suggesting the possibility of meaningful information (recall) bias. Further, in order to obtain sufficient younger controls for comparison purposes, they were required to add more controls to the study using random digit dialing and death certificates. These control selection methods may have resulted in a reference population that was not appropriate for this study and ranked the study quality as low. The Yiin et al. (2012) study similarly found no evidence of a positive association between dicamba exposure and glioma, however, we note that the large number of proxy respondents (45%) for the cases, relative to the controls (3%), was a limitation. Although the study authors mentioned they tried offsetting the number of proxies used by conducting two separate analyses (with and with proxy respondents), inaccurate information obtained from the proxy respondents was still a strong possibility, potentially interfering with estimates of some of the observed outcomes. A third study, Lerro et al. (2020), reported no evidence of a significant positive association in the analysis of intensity weighted lifetime days of use of dicamba among farmers in the AHS prospective cohort. The study was ranked moderate quality and despite benefiting from the strengths of the AHS including the exposure and outcome assessments, the authors did not correct for multiple comparisons in the statistical analysis.

Breast cancer

One publication (Engel et al., 2005) examined the association between dicamba exposure and breast cancer.

- Engel et al. (2005) evaluated the association between breast cancer incidence among farmers' wives and specific pesticides including dicamba. The study population consisted of female spouses of pesticide applicators enrolled in the AHS living in Iowa and North Carolina. Breast cancer cases were identified using cancer registries in Iowa and North Carolina from enrollment (1993-1997) through 2000. Pesticide exposure was assessed based on self-reported questionnaires completed by the AHS participants during study enrollment. Of the 309 breast cancer cases identified within the cohort (n = 30,454), 15 (4.9%) women reported dicamba use. Of the 30,145 non-cases (women not diagnosed with breast cancer) with complete data, a total of 1,146 (3.9%) women reported dicamba use. Poisson regression was used by the authors to calculate RRs and 95% CIs for individual pesticides, and each analysis was adjusted for age, race, and state of residence. The authors reported no evidence of a significant positive association between ever use of dicamba and breast cancer incidence among all wives in the cohort (RR = 1.20; 95% CI: 0.70, 2.00; with 15 exposed cases). A subset analysis conducted for wives who reported no prior pesticide use (n = 13,449) considered husbands' dicamba use and no evidence of a positive association was reported between husband's dicamba use and wife's risk of breast cancer (RR = 1.00; 95% CI: 0.70, 1.50; with 62 cases indirectly exposed).

  The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. As part of the AHS, this study benefited from the strengths of the AHS study cohort as described above. However, the investigators assessed indirect exposure based on self-

reported pesticide use from spouses' husbands, and this approach has not been validated and may not be a reliable proxy for direct dicamba exposure by female spouses. Additionally, there is the potential for misclassification from self-reported previous pesticide exposures.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and breast cancer. One publication (Engel et al., 2005) examined the association between dicamba exposure and breast cancer among female spouses of pesticide applicators in the AHS prospective cohort. Engel et al. (2005) reported no evidence of a significant positive association for direct dicamba exposure and no evidence of a positive association for indirect exposure (measured through husband's ever use of dicamba) and breast cancer. Engel et al. (2005) was ranked moderate quality and benefited from the strengths of the AHS cohort including the prospective design and identification of cancer cases through linkage to state cancer registries. The indirect exposure assessment based on husband's pesticide use was a limitation as it has not been validated and may not be a reliable proxy for direct dicamba exposure by female spouses.

Cancers of the Large Intestine

Three publications (Samanic et al., 2006; Lee et al., 2007; Lerro et al., 2020) examined the relationship between dicamba exposure and cancers of the large intestine including colorectal, rectal, and colon cancers.

Colorectal Cancer

One publication (Lee et al., 2007) examined the relationship between dicamba exposure and colorectal cancer.

- Lee et al. (2007) investigated the association between pesticide exposure, including dicamba, and cancers of the large intestine including colorectal, colon, and rectal cancers using data from the AHS prospective cohort. The study population (n = 56,813) consisted of male pesticide applicators and their spouses living in Iowa and North Carolina who were enrolled in the AHS cohort. Incident cases were identified using state cancer registry files from enrollment (1993-1997) through December 31, 2002 and International Classification of Diseases for Oncology (ICD-0-2) codes. Vital status was confirmed annually through state death registries and the National Death Index. Ever/never exposure to dicamba was assessed through an initial enrollment questionnaire followed by a more detailed self-administered questionnaire filled out at home as part of study enrollment. Unconditional multivariable logistic regression was used to calculate ORs and 95% CIs for dicamba, adjusting for age, smoking, state, and total lifetime days of pesticide application. Among the 305 colorectal cases identified in the study, 110 reported ever exposure to dicamba, and 142 reported never exposure to dicamba (not all cases reported exposure status for dicamba). No evidence of a positive association was reported between exposure to dicamba and colorectal cancer based on ever use (OR = 0.90; 95% CI: 0.70, 1.20; with n = 110 exposed cases and n = 142 unexposed cases).

  The study quality was ranked high based on the study quality criteria provided in the OPP Framework. The prospective cohort study design as part of the AHS, the ascertainment of cancer cases using established registries, and the pesticide exposure assessment were considered strengths of the study.

EPA Conclusion

Overall, there is *no epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and colorectal cancer. One publication (Lee et al., 2007) examined the relationship between dicamba ever exposure and rectal cancer and reported no evidence of a positive association.

Colon Cancer

Three publications (Samanic et al., 2006; Lee et al., 2007; Lerro et al., 2020) examined the relationship between dicamba exposure and colon cancer.

- Samanic et al. (2006) examined the association between dicamba exposure and several cancers, including colon cancer among pesticide applicators in the AHS prospective cohort. The study population included male pesticide applicators living in Iowa and North Carolina who completed the AHS enrollment questionnaires and had complete data on dicamba and covariates. Cases of incident cancer (first primary cancer) diagnosed between enrollment (1993 - 1997) and December 31, 2002 were identified via linkage to state cancer registries. Those who reported cancer at the time of enrollment (n = 1,075) or were missing information about dicamba (n = 6,362); or missing information about covariates (n = 6,608) were excluded from the analysis. Females were excluded from the analysis because there were only four cancer cases among female participants. Pesticide exposure was assessed using responses about pesticide exposure captured on the enrollment questionnaires. Poisson regression was used to estimate individual RRs and 95% CIs, for the association between dicamba exposure and several cancers, adjusting for age, education, state of residence, smoking (pack years), family history of cancer, and total lifetime days of pesticide application. Lifetime exposure days were grouped into tertiles on the basis of the distribution among all cancer cases combined and the highest tertile was divided at the median to create the following categories for lifetime exposure days for all cancer types: No exposure, 1 to < 20 days, 20 to < 56 days, 56 to < 116 days, and ≥ 116 days. For the intensity-weighted lifetime exposure days analysis, categories of exposure included no exposure, 1 to < 86.6, 86.6 to < 344.3, 344.3 to < 739.2, and ≥ 739.2 intensity-weighted days. Among the 41,969 male pesticide applicators included in the analysis, 22,036 (52.5%) reported exposure to dicamba. And, of the 135 colon cancer cases included in the analysis, 59 reported exposure to dicamba. Evidence of a strong association was reported in the highest exposure group for lifetime days of dicamba exposure and colon cancer, *with the low exposure group as the referent (≥ 116 days* – RR = 3.29; 95% CI: 1.40, 7.73; with n = 17 exposed cases). No evidence of a significant positive association was reported for any other exposure level of lifetime days of dicamba use with *low exposed group* or the *no exposure group* as the referent (0.42 < all RRs < 2.07; all 95% CIs encompassed the null value of 1.0; with n = 9 - 20 cases per exposure category; no exposure group as referent p-trend = 0.10, low exposed as referent p-trend = 0.02). Similarly, evidence of a moderately strong positive association was reported in the highest exposure group for intensity-weighted lifetime days of dicamba exposure with the *low exposed group* as the referent (*≥ 739.2 days* – RR = 2.57; 95% CI: 1.28, 5.17; with n = 20 exposed cases). No evidence of a significant positive association was reported for any other exposure category of intensity-weighted lifetime exposure days with the *low exposed group* or the *no exposure group* as the referent (0.50 < all RRs < 1.76; all 95% CIs encompassed the null value of 1.0; with n = 6 - 20 exposed cases per exposure category; no exposure referent p-trend = 0.02, low exposure referent p-trend = 0.002).

  The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The ranking was based on the general strengths of the AHS, including its prospective design, ability to identify cancer cases through linkage to cancer registries, and exposure assessment

approach which examined cumulative lifetime exposure to dicamba. Limitations were noted including the fact that the authors did not correct for/adjust for multiple comparison/multiple testing and that we would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported.

- Lee et al. (2007) investigated the association between pesticide exposure, including dicamba, and cancers of the large intestine including colorectal, colon, and rectal cancers using data from the AHS prospective cohort. The study population (n = 56,813) consisted of male pesticide applicators and their spouses living in Iowa and North Carolina who were enrolled in the AHS cohort. Incident cases were identified using state cancer registry files from enrollment (1993-1997) through December 31, 2002 and International Classification of Diseases for Oncology (ICD-0-2) codes. Vital status was confirmed annually through state death registries and the National Death Index. Ever/never exposure to dicamba was assessed through an initial enrollment questionnaire followed by a more detailed self-administered questionnaire filled out at home as part of study enrollment. Unconditional multivariable logistic regression was used to calculate ORs and 95% CIs for dicamba, adjusting for age, smoking, state, and total lifetime days of pesticide application. Among the 212 colon cancer cases identified in the study, 79 reported ever-exposure to dicamba, and 98 reported never-exposure to dicamba (not all cases reported exposure status for dicamba). No evidence of a positive association was reported between exposure to dicamba and colon cancer, based on ever use (OR = 0.90; 95% CI: 0.60, 1.30; with n = 79 exposed cases and n = 98 unexposed cases).

  The study quality was ranked high based on the study quality criteria provided in the OPP Framework. The prospective cohort study design as part of the AHS, the ascertainment of cancer cases using established registries, and the pesticide exposure assessment were considered strengths of the study.

- In a follow-up study to Samanic et al. (2006), Lerro et al. (2020) investigated the association between dicamba exposure and several cancers including cancers of the colon and rectum using data from the AHS prospective cohort. The study population (n = 49,992) consisted of pesticide applicators living in Iowa and North Carolina who were enrolled in the AHS cohort and who reported information on dicamba exposure at enrollment and follow-up. Incident cancer cases were identified using Iowa and North Carolina state cancer registry files from enrollment (1993-1997) through December 2014 in North Carolina and December 2015 in Iowa. International Classification of Diseases for Oncology (ICD-0-2) codes were used to classify cancer sites. Dicamba exposure was assessed through the enrollment questionnaire (1993 – 1997) and the first follow-up interview five years after enrollment (1999 – 2005). Multiple imputation was used to estimate pesticide exposures at follow-up for individuals who did not complete the interview (n = 20, 968, 37%). Poisson regression was used to calculate relative risks and 95% confidence intervals for each category of intensity-weighted days of dicamba use compared with no use, adjusting for age, race, sex, smoking, state, applicator type, education, imazethapyr use (Spearmen p = 0.49), and family history of cancer. The analysis for cancers of the colon and rectum was also adjusted for BMI. Cumulative intensity-weighted days were categorized as no exposure or quartiles of intensity-weighted days of exposure among all incident cancer cases for sites with > 20 exposed (no use, 5.0 – 449.5 days, 449.6 – 1260.0 days, 1260.1 – 3,698 days, >3,689 days) or based on the median, as no, low or high exposure for cancers and subtypes with 10–20 exposed cases (no use, 5.0 – 1,260.0 days, > 1,260.0 days). Among the 49,922 applicators, 26,412 (52.9%) reported dicamba exposure and among the 513 colon cancer cases and 232 rectal cancer cases, 250 cases of colon cancer and 105 cases of rectal cancer reported dicamba exposure. No evidence of a significant positive association was reported for any exposure category of dicamba and colon cancer (0.78 < RR < 1.01; all 95% CIs encompassed the null value of 1.0; with n

= 59 - 68 exposed cases per exposure category; p-trend = 0.71), with the no exposure group as the referent, and no evidence of a significant exposure-response trend.

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The general strengths of the publication included the underlying prospective design of the AHS, focus on U.S. agricultural populations, and availability of a U.S. cancer registry to comprehensively identify cancer cases. Authors performed multiple comparisons however did not correct for multiple comparison. We would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and colon cancer. Three publications (Samanic et al., 2006; Lee et al., 2007; Lerro et al., 2020) examined the relationship between dicamba exposure and colon cancer. Lee et al. (2007) reported no evidence of a positive association between dicamba ever use and colon cancer. Samanic et al. (2006) investigated the association between dicamba and colon cancer using lifetime exposure days and intensity-weighted lifetime exposure days and exposure-response analysis. Samanic et al. (2006) reported no evidence of a significant positive association between lifetime and intensity weighted exposure days of dicamba in the highest exposure categories and colon cancer, with the no exposure group as the referent. And, authors reported no evidence of a positive association in any other exposure categories of dicamba use and colon cancer. When the low exposure group was used as the referent a strong association for lifetime days of dicamba exposure and a slight positive association for intensity weighted lifetime days of exposure was reported between dicamba and colon cancer, with the low exposure group as the referent. With longer follow-up time and additional cases of colon cancer, Lerro et al. (2020) reported no evidence of a significant positive association between dicamba intensity weighted lifetime days of dicamba use and colon among the large AHS prospective cohort in Iowa and North Carolina. Both studies were determined to be moderate quality and while the outcome and exposure assessments were strong, a notable limitation was the multiple comparisons that were made without statistical correction.

Rectal Cancer

Two publications (Lee et al., 2007; Lerro et al., 2020) examined the relationship between dicamba exposure and rectal cancer.

- Lee et al. (2007) investigated the association between pesticide exposure, including dicamba, and cancers of the large intestine including colorectal, colon, and rectal cancers using data from the AHS prospective cohort. The study population (n = 56,813) consisted of male pesticide applicators and their spouses living in Iowa and North Carolina who were enrolled in the AHS cohort. Incident cases were identified using state cancer registry files from enrollment (1993-1997) through December 31, 2002 and International Classification of Diseases for Oncology (ICD-0-2) codes. Vital status was confirmed annually through state death registries and the National Death Index. Ever/never exposure to dicamba was assessed through an initial enrollment questionnaire followed by a more detailed self-administered questionnaire filled out at home as part of study enrollment. Unconditional multivariable logistic regression was used to calculate ORs and 95% CIs for dicamba, adjusting for age, smoking, state, and total lifetime days of pesticide application. Among the 93 cases of rectal cancer identified in the study, 31 reported ever exposure to dicamba, and 44 reported never exposure to dicamba (not all cases reported exposure status for dicamba). No evidence of a positive association was reported

between exposure to dicamba and rectal cancer based on ever use (OR = 0.80; 95% CI: 0.50, 1.40; with n = 31 exposed cases and n = 44 unexposed cases).

The study quality was ranked high based on the study quality criteria provided in the OPP Framework. The prospective cohort study design as part of the AHS, the ascertainment of cancer cases using established registries, and the pesticide exposure assessment were considered strengths of the study.

- Lerro et al. (2020) investigated the association between dicamba exposure and several cancers including cancers of the colon and rectum using data from the AHS prospective cohort. The study population (n = 49,992) consisted of pesticide applicators living in Iowa and North Carolina who were enrolled in the AHS cohort and who reported information on dicamba exposure at enrollment and follow-up. Incident cancer cases were identified using Iowa and North Carolina state cancer registry files from enrollment (1993-1997) through December 2014 in North Carolina and December 2015 in Iowa. International Classification of Diseases for Oncology (ICD-0-2) codes were used to classify cancer sites. Dicamba exposure was assessed through the enrollment questionnaire (1993 – 1997) and the first follow-up interview five years after enrollment (1999 – 2005). Multiple imputation was used to estimate pesticide exposures at follow-up for individuals who did not complete the interview (n = 20, 968, 37%). Poisson regression was used to calculate relative risks and 95% confidence intervals for each category of intensity-weighted days of dicamba use compared with no use, adjusting for age, race, sex, smoking, state, applicator type, education, imazethapyr use (Spearmen p = 0.49), and family history of cancer. The analysis for cancers of the colon and rectum was also adjusted for BMI. Cumulative intensity-weighted days were categorized as no exposure or quartiles of intensity-weighted days of exposure among all incident cancer cases for sites with > 20 exposed (no use, 5.0 – 449.5 days, 449.6 – 1260.0 days, 1260.1 – 3,698 days, >3,689 days) or based on the median, as no, low or high exposure for cancers and subtypes with 10–20 exposed cases (no use, 5.0 – 1,260.0 days, > 1,260.0 days). Among the 49,922 applicators, 26,412 (52.9%) reported dicamba exposure and among the 513 colon cancer cases and 232 rectal cancer cases, 250 cases of colon cancer and 105 cases of rectal cancer reported dicamba exposure. No evidence of a positive association was reported for any exposure category of dicamba and rectal cancer ($0.65 < RR < 0.91$; all 95% CIs encompassed the null value of 1.0; with n = 22 - 31 exposed cases per exposure category; p-trend = 19), with the no exposure group as the referent, and no evidence of a significant exposure-response trend.

  The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The general strengths of the publication included the underlying prospective design of the AHS, focus on U.S. agricultural populations, and availability of a U.S. cancer registry to comprehensively identify cancer cases. Authors performed multiple comparisons however did not correct for multiple comparison. We would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported.

EPA Conclusion

Overall, there is *no epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and rectal cancer. Two publications (Lee et al., 2007; Lerro et al., 2020) examined the relationship between dicamba exposure and rectal cancer. Lee et al. (2007) reported no evidence of a positive association between ever use of dicamba and rectal cancer. Lerro et al. (2020) reported no evidence of a positive association between intensity-weighted lifetime days of dicamba use and rectal cancer.

Esophageal Cancer

Two publications (Lee et al., 2004; Lerro et al., 2020) examined the association between dicamba and esophageal cancer.

- Lee et al. (2004) investigated the association between farming and agricultural pesticide use, including dicamba, and stomach and esophageal cancers in the Nebraska Health Study II, a case-control study of adults in eastern Nebraska. The study population included white residents of eastern Nebraska, ≥21 years old. Cases of incident stomach and esophageal adenocarcinoma were identified using the Nebraska Cancer Registry (1988 – 1990) and discharge and pathology records from 14 participating hospitals Nebraska. Controls for the current study were randomly selected from the control group of a previous study covering the same base population investigating lymphohematopoietic cancers (<65 years – random digit dialing, ≥65 years – Medicare files, for deceased cases – Nebraska mortality records) and were frequency matched by age, gender, and vital status to the combined distribution of the glioma, stomach, and esophagus cancer cases. Demographic, medical and family history, occupational, and, pesticide exposure information (for those who lived or worked on farm) was collected via telephone interview conducted during 1992-1994. Pesticide exposure information was limited to use prior to 1985, the time period of the previous study. Interviews were conducted for 170 stomach cancer cases, 137 esophageal cancer cases and 502 controls, however most interviews were conducted via proxy (76% of esophageal adenocarcinoma cases, 80% of stomach cancer cases, 61% of controls) who were primarily spouses or other primary relatives. Unconditional logistic regression was used to calculate ORs and 95% CIs for farming activity and for individual pesticide use, adjusted for age and gender, with the non-farmers as a reference group. Among the 137 esophageal cancer cases and 502 controls included in the final analysis, 13 esophageal cancer cases and 35 controls reported dicamba exposure. No evidence of a positive association was reported for dicamba ever use and esophageal cancer among farmers in Nebraska, among a small number of cases (OR = 0.90; 95% CI: 0.50, 1.90; with n = 13 exposed cases).

  The quality of the study was ranked low quality based on the study quality criteria provided in the OPP framework. The study had several important limitations related to its design, exposure assessment approach, statistical analysis, and ability to control for confounding. With regard to study design, Lee et al. (2005) used a case-control approach and may have introduced selection bias when recruiting their control group. Differences between the results for the self-reporting respondents and the proxy respondents illustrate the possible problem, as the control groups for each of these respondents were constructed differently and each could be biased in a different way. In the analysis, the reference group for the statistical tests was non-farmers, even though the pesticide use questions were not asked of non-farmers. As a result, the results for pesticides are confounded with farmer versus non-farmers and control groups with different proportions of farmers will result in different statistical results. The use of respondent-reported dicamba use to ascertain exposure introduced further uncertainty because it is not possible to attribute the increased odds of glioma to dicamba exposure alone. In particular, the self-reporting and proxy respondents have different levels of knowledge about pesticide use and possibly different motives for responding. Moreover, self-reported exposure assessment is likely to be subject to differential misclassification because study participants may incorrectly recall previous pesticide usage. In addition to these limitations, findings on dicamba are based on a small number of exposed cases which restricts the ability to interpret with confidence the observed odds ratios

- Lerro et al. (2020) investigated the association between dicamba exposure and several cancers including esophageal cancer using data from the AHS prospective cohort. The study population (n =

49,992) consisted of pesticide applicators living in Iowa and North Carolina who were enrolled in the AHS cohort and who reported information on dicamba exposure at enrollment and follow-up. Incident cancer cases were identified using Iowa and North Carolina state cancer registry files from enrollment (1993-1997) through December 2014 in North Carolina and December 2015 in Iowa. International Classification of Diseases for Oncology (ICD-0-2) codes were used to classify cancer sites. Dicamba exposure was assessed through the enrollment questionnaire (1993 – 1997) and the first follow-up interview five years after enrollment (1999 – 2005). Multiple imputation was used to estimate pesticide exposures at follow-up for individuals who did not complete the interview (n = 20, 968, 37%). Poisson regression was used to calculate relative risks and 95% confidence intervals for each category of intensity-weighted days of dicamba use compared with no use, adjusting for age, race, sex, smoking, state, applicator type, education, imazethapyr use (Spearmen p = 0.49), and family history of cancer. The analysis for stomach cancer was also adjusted for pack-years smoked (tertiles by smoking status), alcohol consumption, and BMI. Cumulative intensity-weighted days were categorized as no exposure or quartiles of intensity-weighted days of exposure among all incident cancer cases for sites with > 20 exposed (no use, 5.0 – 449.5 days, 449.6 – 1260.0 days, 1260.1 – 3,698 days, >3,689 days) or based on the median, as no, low or high exposure for cancers and subtypes with 10–20 exposed cases (no use, 5.0 – 1,260.0 days, > 1,260.0 days). Among the 49,922 applicators, 26,412 (52.9%) reported dicamba exposure and among the 102 cases of stomach cancer, 58 reported dicamba exposure. Evidence of a positive association was reported for the third exposure category (*1260.1 – 3,698 days* - OR = 1.99; 95% CI: 1.10, 3.59; with n = 23 exposed cases). No evidence of a positive association was reported for any other exposure category (0.96 < RR < 0.99; all 95% CIs encompassed the null value of 1.0; with n = 10 - 14 exposed cases per exposure category; p-trend = 1.00), with the no exposure group as the referent, and no evidence of a significant exposure-response trend.

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The general strengths of the publication included the underlying prospective design of the AHS, focus on U.S. agricultural populations, and availability of a U.S. cancer registry to comprehensively identify cancer cases. Authors performed multiple comparisons however did not statistically correct for multiple comparisons. We would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a causal or clear associative relationship between dicamba exposure and esophageal cancer. Two studies (Lee et al., 2004; Lerro et al., 2020) examined the association between dicamba exposure and esophageal cancer. Lee et al. (2004) reported no evidence of a positive association among farmers in Nebraska and was low quality due to several limitations including the study design, control selection, and comparison of farmers to nonfarmers, and the large number of proxy respondents. Lerro et al. (2020) reported evidence of a positive association between intensity-weighted exposure days of dicamba and esophageal cancer in the third exposure category and no evidence of a positive association in the first, second, and fourth exposure categories. Lerro et al., (2020) also reported no evidence of an exposure-response trend among the AHS cohort. Lerro et al. (2020) was moderate quality and while the outcome and exposure assessments were strong, a notable limitation was the multiple comparisons without statistical correction where several significant associations would likely no longer be significant after statistical correction.

Cancer of the Larynx

One publication (Lerro et al., 2020) examined the association between dicamba and laryngeal cancer.

Lerro et al. (2020) investigated the association between dicamba exposure and several cancers including cancer of the larynx using data from the AHS prospective cohort. The study population (n = 49,992) consisted of pesticide applicators living in Iowa and North Carolina who were enrolled in the AHS cohort and who reported information on dicamba exposure at enrollment and follow-up. Incident cancer cases were identified using Iowa and North Carolina state cancer registry files from enrollment (1993-1997) through December 2014 in North Carolina and December 2015 in Iowa. International Classification of Diseases for Oncology (ICD-0-2) codes were used to classify cancer sites. Dicamba exposure was assessed through the enrollment questionnaire (1993 – 1997) and the first follow-up interview five years after enrollment (1999 – 2005). Multiple imputation was used to estimate pesticide exposures at follow-up for individuals who did not complete the interview (n = 20, 968, 37%). Poisson regression was used to calculate relative risks and 95% confidence intervals for each category of intensity-weighted days of dicamba use compared with no use, adjusting for age, race, sex, smoking, state, applicator type, education, imazethapyr use (Spearmen p = 0.49), and family history of cancer. The analysis for lip cancer was also adjusted for pack-years smoked (tertiles by smoking status). Cumulative intensity-weighted days were categorized as no exposure or quartiles of intensity-weighted days of exposure among all incident cancer cases for sites with > 20 exposed (no use, 5.0 – 449.5 days, 449.6 – 1260.0 days, 1260.1 – 3,698 days, >3,689 days) or based on the median, as no, low or high exposure for cancers and subtypes with 10–20 exposed cases (no use, 5.0 – 1,260.0 days, > 1,260.0 days). Among the 49,922 applicators, 26,412 (52.9%) reported dicamba exposure and among the 60 cases of laryngeal cancer, 23 reported dicamba exposure. No evidence of a positive association was reported for any exposure category (0.43 < RR < 0.80; all 95% CIs encompassed the null value of 1.0; with n = 5 – 8 cases per exposure category; p-trend = 0.44), with the no exposure group as the referent, and no evidence of a significant exposure-response trend.

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The general strengths of the publication included the underlying prospective design of the AHS, focus on U.S. agricultural populations, and availability of a U.S. cancer registry to comprehensively identify cancer cases. Authors performed multiple comparisons however did not correct for multiple comparison. We would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported.

EPA Conclusion

Overall, there is *no epidemiological evidence* at this time to conclude that there is a causal or clear associative relationship between dicamba exposure and cancer of the larynx. One study (Lerro et al., 2020) examined the association between intensity weighted lifetime days of dicamba use and cancer of the larynx and reported no evidence of a significant positive association among AHS participants. Lerro et al. (2020) was deemed moderate quality for regulatory purposes and while the outcome and exposure assessments were strong, a notable limitation was the multiple comparisons without statistical correction.

Lip Cancer

One publication (Lerro et al., 2020) examined the association between dicamba and lip cancer.

Lerro et al. (2020) investigated the association between dicamba exposure and several cancers including lip cancer using data from the AHS prospective cohort. The study population (n = 49,992) consisted of

pesticide applicators living in Iowa and North Carolina who were enrolled in the AHS cohort and who reported information on dicamba exposure at enrollment and follow-up. Incident cancer cases were identified using Iowa and North Carolina state cancer registry files from enrollment (1993-1997) through December 2014 in North Carolina and December 2015 in Iowa. International Classification of Diseases for Oncology (ICD-0-2) codes were used to classify cancer sites. Dicamba exposure was assessed through the enrollment questionnaire (1993 – 1997) and the first follow-up interview five years after enrollment (1999 – 2005). Multiple imputation was used to estimate pesticide exposures at follow-up for individuals who did not complete the interview (n = 20, 968, 37%). Poisson regression was used to calculate relative risks and 95% confidence intervals for each category of intensity-weighted days of dicamba use compared with no use, adjusting for age, race, sex, smoking, state, applicator type, education, imazethapyr use (Spearmen p = 0.49), and family history of cancer. The analysis for lip cancer was also adjusted for pack-years smoked (tertiles by smoking status and non-combustible tobacco use. Cumulative intensity-weighted days were categorized as no exposure or quartiles of intensity-weighted days of exposure among all incident cancer cases for sites with > 20 exposed (no use, 5.0 – 449.5 days, 449.6 – 1260.0 days, 1260.1 – 3,698 days, >3,689 days) or based on the median, as no, low or high exposure for cancers and subtypes with 10–20 exposed cases (no use, 5.0 – 1,260.0 days, > 1,260.0 days). Among the 49,922 applicators, 26,412 (52.9%) reported dicamba exposure and among the 54 cases of lip cancer, 30 reported dicamba exposure. No evidence of a significant positive association was reported for any exposure category (0.50 < RR < 1.07; all 95% CIs encompassed the null value of 1.0; with n = 5 – 10 exposed cases per exposure category; p-trend = 0.44), with the no exposure group as the referent, and no evidence of a significant exposure-response trend.

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The general strengths of the publication included the underlying prospective design of the AHS, focus on U.S. agricultural populations, and availability of a U.S. cancer registry to comprehensively identify cancer cases. Authors performed multiple comparisons however did not correct for multiple comparison. We would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported.

EPA Conclusion

Overall, there is *insufficient epidemiological* evidence at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and lip cancer. One study (Lerro et al., 2020) examined the association between dicamba exposure and lip cancer. Lerro et al. (2020) reported no evidence of a significant positive association between dicamba intensity weighted lifetime days of dicamba use and lip cancer among the large AHS prospective cohort in Iowa and North Carolina. Lerro et al. (2020) was deemed moderate quality for regulatory purposes and while the outcome and exposure assessments were strong, a notable limitation was the multiple comparisons without statistical correction.

Liver and Intrahepatic Bile Duct Cancers

One study (Lerro et al., 2020) examined the potential association between dicamba exposure and liver and intrahepatic bile duct cancers.

Lerro et al. (2020) investigated the association between dicamba exposure and several cancers including liver and intrahepatic bile duct cancers using data from the AHS prospective cohort. The study population (n = 49,992) consisted of pesticide applicators living in Iowa and North Carolina who were enrolled in the AHS cohort and who reported information on dicamba exposure at enrollment and follow-up. Incident cancer cases were identified using Iowa and North Carolina state cancer registry files from enrollment (1993-1997) through December 2014 in North Carolina and December 2015 in Iowa. International

Classification of Diseases for Oncology (ICD-0-2) codes were used to classify cancer sites. Dicamba exposure was assessed through the enrollment questionnaire (1993 – 1997) and the first follow-up interview five years after enrollment (1999 – 2005). Multiple imputation was used to estimate pesticide exposures at follow-up for individuals who did not complete the interview (n = 20, 968, 37%). Poisson regression was used to calculate relative risks and 95% confidence intervals for each category of intensity-weighted days of dicamba use compared with no use, adjusting for age, race, sex, smoking, state, applicator type, education, imazethapyr use (Spearmen p = 0.49), and family history of cancer. The analysis for liver and intrahepatic bile duct cancers was also adjusted for alcohol consumption and body mass index. Cumulative intensity-weighted days were categorized as no exposure or quartiles of intensity-weighted days of exposure among all incident cancer cases for sites with > 20 exposed (no use, 5.0 – 449.5 days, 449.6 – 1260.0 days, 1260.1 – 3,698 days, >3,689 days) or based on the median, as no, low or high exposure for cancers and subtypes with 10–20 exposed cases (no use, 5.0 – 1,260.0 days, > 1,260.0 days). Among the 49,922 applicators, 26,412 (52.9%) reported dicamba exposure and among the 71 cases of liver and intrahepatic bile duct cancers combined, 28 reported dicamba exposure. Evidence of a positive association was reported in the highest exposure category for cumulative intensity-weighted days of dicamba exposure and liver and intrahepatic bile duct cancers, among a very small number of cases (*>3,689.0 days* – RR = 1.80; 95% CI: 1.26, 2.56; with n = 10 exposed cases). No evidence of a significant positive association was reported for the two middle exposure categories, among a very small number of cases (1.15 < RR < 1.38; all 95% CIs encompassed the null value of 1.0; with n = 6 – 8 exposed cases per exposure category), with the no exposure group as the referent. And, a significant inverse association was reported for the lowest exposure category among a very small number of exposed cases (*5.0 – 449.5 days* - RR = 0.32; 95% CI: 0.18, 0.57; with n = 4 exposed cases). The exposure-response trend was significant (p-trend < 0.001). When the associations between cumulative intensity-weighted days of dicamba exposure and liver cancer and intrahepatic bile duct cancers were examined separately, two exposure categories were created (5.0–1,260.0 days and >1,260.0 days) based on the median as there were fewer than 10 – 20 cases for each type of cancer. No evidence of a significant positive association was reported for *liver cancer* for either exposure category, among a very small number of cases (*5.0–1,260.0 days* – RR = 0.53; 95% CI: 0.19, 1.48; with n = 5 exposed cases; *>1,260.0 days* – RR = 1.04; 95% CI: 0.46, 2.34; with n = 13 exposed cases; p-trend ≥ 0.64), when compared to the referent of no exposure. For *intrahepatic bile duct cancer*, evidence of a moderately strong positive association was reported for the >1,260.0 days exposure category and no evidence of a significant positive association was reported for the 5.0–1,260.0 days exposure category, among a very small number of cases (*5.0 – 1,260.0 days* – RR = 1.74; 95% CI: 0.99, 3.08; with n = 5 exposed cases; *> 1,260.0 days* – RR = 2.92; 95% CI: 1.71, 5.01; with n = 5 exposed cases; p-trend < 0.001).

In an additional analysis for liver and bile duct cancers combined, that examined latency using cumulative intensity-weighted days of exposure with four exposure categories for each 10 and 20 year lag times, (10-year lag: 5.0–396.0, 396.1–1,120.0, 1,120.1–3,315.0. , >3,3150; and 20-year lag: 0 5.0–315.0, 315.1–937.5, 937.6–2,800.0, >2,800.0) evidence of a positive association was reported for the higher levels of exposure for the 10-year lag time (*>3,3150 days* – RR = 1.80; 95% CI: 1.32, 2.43; with n = 12 exposed cases; p-trend <0.001) and for the middle and high exposure categories of the 20-year lag analysis (*>2,800.0 days* – RR = 1.91; 95% CI: 1.39, 2.63; with n = 11 exposed cases; *937.6–2,800.0 days* – RR = 1.76; 95% CI: 1.26, 2.45; with n = 4 exposed cases; p-trend < 0.0001), among a small number of cases. No evidence of a significant positive association was reported for any of the other exposure categories for either the 10-year or the 20-year lag time analyses among a very small number of cases (0.45 < all RRs < 1.34; all 95% CIs encompassed the null value of 1.0; with n = 2 – 8 cases per exposure category).

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The general strengths of the publication included the underlying prospective design of AHS, focus on U.S. agricultural populations, and availability of a U.S. registry to comprehensively

identify cancer cases. Limitations were noted including the fact that the authors did not correct for/adjust for multiple comparison/multiple testing and that we would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported. We also note that the number of exposed cases per exposure category for several of the significant findings was very small (n ≤10) and this may have contributed to the significant inverse association at the low exposure and the significant positive association observed at the high exposure level for both liver and intrahepatic bile duct cancers combined. Finally, the dicamba and liver and intrahepatic bile duct cancer association is a first time (exploratory) finding and AHS practice is to require a second follow-on confirmatory finding to begin to consider making any conclusions. This latter point is acknowledged by the study authors who conclude that future epidemiologic work on dicamba should focus on replication of their study findings.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and liver and intrahepatic bile duct cancers. One study (Lerro et al., 2020) reported evidence of a positive association in the highest exposure category for cumulative intensity-weighted days of exposure among a very small number of cases, and a significant exposure response-trend, the a significant negative association was reported in the lowest exposure category, among a very small number of cases. Significant association were also reported for the 10- and 20-year lagged analyses. While the study had several strengths including the prospective study design, use of cancer registries to ascertain cases, and a validated questionnaire to assess pesticide exposure, several limitations were noted. In particular, over 40 different cancer analyses were performed and no adjustments for multiple comparisons were made. We would expect several of the statistically significant results would no longer remain significant after appropriate adjustments that would account for multiple comparisons. And, we noted several concerns with respect to confounder adjustments that suggest there may be issues with samples size and/or the statistical analysis. Also, the reported association between dicamba exposure and liver and intrahepatic bile duct cancers are first time (exploratory) findings and AHS practice is to require a second follow-on confirmatory finding to begin to consider making any conclusions. This latter point is acknowledged by the study authors who conclude that future epidemiologic work on dicamba should focus on replication of their study findings.

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Lung cancer

Four studies (Alavanja et al., 2004; Samanic et al., 2006; Bonner et al., 2017; Lerro et al., 2020) examined the potential association between dicamba exposure and lung cancer.

- Alavanja et al. (2004) investigated the association between lung cancer incidence and lifetime pesticide exposure, including dicamba, in the AHS prospective cohort. The study population consisted of pesticide applicators (N = 57,284) and spouses (N = 32,333) of pesticide applicators (commercial applicators were excluded due to too few cases) with no history of lung cancer at enrollment, living in Iowa and North Carolina. Incident lung cancer cases were identified through state cancer registries and state death registries and the National Death Index from enrollment (1993-1997) through 2001. Pesticide exposure was assessed via self-administered questionnaires completed during study enrollment (1993 – 1997). Unconditional logistic regression was used to investigate the association between lifetime use and intensity-weighted lifetime days of use of dicamba and lung cancer, adjusting for age, gender, smoking history by pack-years of current and former smokers, and total days of application of any pesticide with two reference groups; those with no exposure and those with low exposure (never users excluded). Dicamba exposure was divided into three tertiles with the top tertile divided in half to create th

- e following categories of dicamba use (lifetime days of use): <24.5 days; 24.5 – 108.5 days; 108.6 – 224.7 days; and, >224.7 days for the exposure-response analysis. In the analysis comparing tertiles of lifetime days of dicamba use with the *low exposure group as the referent*, evidence of a strong association was reported in the highest exposure category among a very small number of cases (*>224.7 days* – OR = 3.10, 95% CI 1.27, 7.70, with n = 8 exposed). No evidence of a significant positive association was reported in any other exposure category for lifetime use with the low exposure group as the referent (1.3 < all other ORs < 1.7; all CIs encompassed the null value of 1.0; with 8– 19 cases per category, and p-trend 0.04). For the lifetime days of use exposure-response analysis with the *no exposure group as the referent*, no evidence of a significant positive association was reported in any exposure category (0.70 < all other ORs < 1.60; all 95% CIs encompassed the null value of 1.0; with 8 – 21 cases per exposure category; p-trend = 0.15). Results for the intensity-weighted days of dicamba exposure analysis were not reported.

  The quality of the study was ranked high based on the study quality criteria provided in the OPP Framework. The ranking was based on the general strengths of the AHS, including its prospective design, ability to identify cancer cases through linkage to cancer registries, and exposure assessment approach which examined cumulative lifetime exposure to dicamba. We note that the number of cases of lung cancer with dicamba exposure were very small in some exposure categories.

- Samanic et al. (2006) examined the association between dicamba exposure and several cancers, including lung cancer among pesticide applicators in the AHS prospective cohort. The study population included male pesticide applicators living in Iowa and North Carolina who completed the AHS enrollment questionnaires and had complete data on dicamba and covariates. Cases of incident cancer (first primary cancer) diagnosed between enrollment (1993 - 1997) and December 31, 2002 were identified via linkage to state cancer registries. Those who reported cancer at the time of enrollment (n = 1,075) or were missing information about dicamba (n = 6,362); or missing information about covariates (n = 6,608) were excluded from the analysis. Females were excluded from the analysis because there were only four cancer cases among female participants. Pesticide exposure was assessed using responses about pesticide exposure captured on the enrollment questionnaires. Poisson regression was used to estimate individual RRs and 95% CIs, for the association between dicamba exposure and several cancers, adjusting for age, education, state of residence, smoking (pack years), family history of cancer, and total lifetime days of pesticide application. Lifetime exposure days were grouped into tertiles on the basis of the distribution among all cancer cases combined and the highest tertile was divided at the median to create the following categories for lifetime exposure days for all cancer types: No exposure, 1 to < 20 days, 20 to < 56 days, 56 to < 116 days, and ≥ 116 days. For the intensity-weighted lifetime exposure days analysis, categories of exposure included no exposure, 1 to < 86.6, 86.6 to < 344.3, 344.3 to < 739.2, and ≥ 739.2 intensity-weighted days. Among the 41,969 male pesticide applicators included in the analysis, 22,036 (52.5%) reported exposure to dicamba. Of the 147 lung cancer cases included in the analysis, 52 reported exposure to dicamba. No evidence of a significant positive association was reported for lifetime days of dicamba exposure at all exposure levels with the no exposed group and the low exposure group as the referent (0.64 < all RRs < 2.16; all 95% CIs encompassed the null value of 1.0; with n = 11 - 15 cases per exposure category; no exposed referent p-trend = 0.13, low exposed as referent p-trend = 0.02). Similarly, no evidence of a significant positive association was reported for all exposure categories of intensity-weighted lifetime exposure days with the no exposed group and the low exposure group as the referent (0.61 < all RRs < 2.20; all 95% CIs encompassed the null value of 1.0; with n = 10 - 20 exposed cases per exposure category; all p-trends > 0.05).

  The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The ranking was based on the general strengths of the AHS, including its prospective

design, ability to identify cancer cases through linkage to cancer registries, and exposure assessment approach which examined cumulative lifetime exposure to dicamba. Limitations were noted including the fact that the authors did not correct for/adjust for multiple comparison/multiple testing and that we would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported.

- Bonner et al. (2017) investigated the potential association between pesticides such as dicamba and incident lung cancer using data from the AHS prospective cohort. The study population (n = 57,310) consisted of pesticide applicators living in Iowa and North Carolina, and pesticide exposure was assessed through two self-administered questionnaires completed at study enrollment and at home (1993 – 1997). Exposure information was updated through a follow-up questionnaire using a computer-assisted telephone interview between 1999 – 2005. Cases included AHS study participants who self-reported incident lung cancer between study enrollment up to December 31, 2010 in North Carolina and December 31, 2011 in Iowa. Cases were ascertained through cancer registries in Iowa and North Carolina, and vital status was confirmed using the state and national death databases. Cox proportional hazards regression was used to calculate HRs and 95% CIs for dicamba and incident lung cancer, adjusting for smoking status and pack-years, age, sex, and total lifetime pesticide use. Tertiles[18] were constructed based on lifetime days and intensity-weighted lifetime-days of exposure, and HRs were reported for each tertile. No evidence of a positive association was reported between dicamba and lung cancer at any exposure level for lifetime or intensity weighted lifetime days of exposure ($0.57 <$ all HRs < 0.86; all CIs encompassed the null value of 1.0; with n = 36 – 45 exposed cases per exposure category; p-trends < 0.05). Dicamba showed a statistically significant inverse association with lung cancer in the two lowest exposure groups for both lifetime and intensity weighted lifetime days and significant exposure–response trends. Similar findings of significant inverse associations were reported in sensitivity analyses that considered 5- and 15-year lagged lifetime exposure days.

  The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The ranking was based on the general strengths of the AHS, including its prospective design, ability to identify and ascertain cancer cases through linkage to cancer registries, and exposure assessment approach which examined lifetime days of exposure and intensity-weighted lifetime days of exposure to dicamba. One of the study limitations included a large percentage of missing exposure data during the follow-up period (37% of the participants did not complete the follow-up interview). The authors imputed the missing exposure data for subjects who did not complete the follow-up interview using multiple imputation, which is the considered state-of-the-science for dealing with missing data.[19] The authors did not mention nor discuss any sensitivity analyses where only the data of completed subjects were analyzed. Additionally, details regarding the duration of time for each exposure quartile (e.g., days, months, years) were not provided but would have been helpful.

- Lerro et al. (2020) investigated the association between dicamba exposure and several cancers including lung cancer using data from the AHS prospective cohort that included additional cases,

[18] Pesticide exposure (split into tertiles or quartiles) was not defined for specific pesticides within the tables reported by Bonner et al. (2017).

[19] Note that the authors did not incorporate the information of lung cancer in the process of imputing the missing exposure values (as it appears in the reference provided by the authors), and this might result in a bias toward the null for any reported estimates. However, the missing exposure data for dicamba of subjects who did not complete the follow-up questionnaire were imputed based on the available information for factors that related to pesticide use such as demographic, medical history, other farm characteristics, and reported pesticide use at enrollment, and it would thus be expected that the impact of failing to include the lung cancer information would not be to substantially affect the estimated effect sizes.

exposure information, and longer follow-up time. The study population (n = 49,992) consisted of pesticide applicators living in Iowa and North Carolina who were enrolled in the AHS cohort and who reported information on dicamba exposure at enrollment and follow-up. Incident cancer cases were identified using Iowa and North Carolina state cancer registry files from enrollment (1993-1997) through December 2014 in North Carolina and December 2015 in Iowa. International Classification of Diseases for Oncology (ICD-0-2) codes were used to classify cancer sites. Dicamba exposure was assessed through the enrollment questionnaire (1993 – 1997) and the first follow-up interview five years after enrollment (1999 – 2005). Multiple imputation was used to estimate pesticide exposures at follow-up for individuals who did not complete the interview (n = 20, 968, 37%). Poisson regression was used to calculate relative risks and 95% confidence intervals for each category of intensity-weighted days of dicamba use compared with no use, adjusting for age, race, sex, smoking, state, applicator type, education, imazethapyr use (Spearmen p = 0.49), and family history of cancer. The analysis for lung cancer was also adjusted for smoking (packed years). Cumulative intensity-weighted days were categorized as no exposure or quartiles of exposure among all incident cancer cases for sites with > 20 exposed (no use, 5.0 – 449.5 days, 449.6 – 1260.0 days, 1260.1 – 3,698 days, >3,689 days) or based on the median, as no, low or high exposure for cancers and subtypes with 10–20 exposed cases (no use, 5.0 – 1,260.0 days, > 1,260.0 days). Among the 49,922 applicators, 26,412 (52.9%) reported dicamba exposure and among the 689 cases of lung cancer, 240 reported dicamba exposure. No evidence of a positive association was reported for lung cancer (all subtypes included) for any exposure category of cumulative intensity-weighted days of use (0.60 < RR < 0.80; all 95% CIs encompassed the null value of 1.0; with n = 58 - 61 exposed cases per category, p-trend > 0.05). For the histological subtypes of lung cancer characterized in this study, including Small Cell, Squamous Cell, and Adenocarcinoma, no evidence of a significant positive association was reported for any exposure category and no evidence of a significant exposure-response trend (0.30 < RR < 1.05; all 95% CI: encompassed the null value of 1.0; with n = 5 - 24 exposed cases per exposure category; all p-trends > 0.05). We note that several exposure categories among lung cancer histological subtypes had a small number of cases. In an additional analysis to address latency, where cumulative intensity-weighted days of exposure for each year of follow-up was determined, no evidence of a positive association was reported for any exposure category for either the 10-year or 20-year exposure lag (0.65 < all RRs < 0.88; all 95% CIs encompassed the null value of 1.0; with n = 35 - 61 exposed cases per exposure category; p-trends > 0.05) when compared to no exposure, and no evidence of an exposure-response trend.

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The general strengths of the publication included the underlying prospective design of AHS, focus on U.S. agricultural populations, and availability of a U.S. registry to comprehensively identify cancer cases. Lerro et al. (2020) indirectly assessed dicamba exposure based on the AHS survey instrument. Limitations were noted including the fact that the authors did not correct for/adjust for multiple comparison/multiple testing and that we would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported. We also note that the number of exposed cases per exposure category for several of the significant findings was small (n = 10).

EPA Conclusion

Overall, there is *insufficient epidemiological* evidence at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and lung cancer. There were four available publications (Alavanja et al., 2004; Samanic et al., 2006; Bonner et al., 2017; Lerro et al., 2020) and all used data from the AHS prospective cohort, to examine the association between dicamba exposure and lung cancer among male pesticide applicators. Early studies reported evidence of an association however,

this association was no longer significant with longer follow-up time and increasing number of cases. The first study, Alavanja et al. (2004) reported evidence of a strong positive association between dicamba exposure and lung cancer at the highest exposure level, with the low exposed group as the referent, among a very small number of cases (n = 8). Authors reported no evidence of a significant positive association for all exposure categories with the no exposed group as the referent and for any other exposure category for with the low exposure group as the referent. We note also that a small number of cases reported exposure to dicamba overall and that resulted in a very small number of cases in several exposure categories, including the category with the significant association, which severely restricts the interpretability of the observed odds ratios. Alavanja et al. (2004) was ranked high quality. The second publication, Samanic et al. (2006) reported no evidence of a significant positive association between dicamba exposure and lung cancer for either lifetime or intensity-weighted days of exposure. The quality of the study was ranked moderate. The third publication, Bonner et al. (2017), reported no evidence of a significant positive association between dicamba exposure and lung cancer for either lifetime days or intensity-weighted days of exposure. The quality of the study was ranked moderate. Study limitations included the high percentage of missing data (37%, n = 20,968) on the enrollment and follow-up questionnaires, and the small number of study participants (44%) who completed the take-home questionnaire at enrollment for the remaining 28 pesticides that had not been covered during the initial portion of the questionnaire. Finally, the fourth publication, Lerro et al., (2020), reported no evidence of a positive association between dicamba and lung cancer at any exposure level of intensity-weighted exposure days with longer follow-up time, additional exposure information and additional cases than the three previous studies. The study was ranked moderate and limitations included the multiple comparisons without adjustment. Results from the ever/never use analysis were not reported.

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Lymphohematopoietic Cancers

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Fifteen publications (Brown et al., 1990; Cantor et al., 1992; Brown et al., 1993; McDuffie et al., 2001; De Roos et al., 2003; Hartge et al., 2005; McDuffie et al., 2005; Pahwa et al., 2006; Samanic et al., 2006; Pahwa et al., 2012; Metayer et al., 2013; Czarnota et al., 2015; Leon et al., 2019; Latifovic et al., 2020; Lerro et al., 2020) investigated the potential association between dicamba exposure and lymphohematopoietic cancers including, hematopoietic cancer, leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, and subtypes including multiple myeloma.

Hematopoietic Cancers

One study (Samanic et al., 2006) examined the potential association between dicamba exposure and hematopoietic cancers combined.

Samanic et al. (2006) examined the association between dicamba exposure and several cancers, including all hematopoietic cancers among pesticide applicators in the AHS prospective cohort. The study population included male pesticide applicators living in Iowa and North Carolina who completed the AHS enrollment questionnaires and had complete data on dicamba and covariates. Cases of incident cancer (first primary cancer) diagnosed between enrollment (1993 - 1997) and December 31, 2002 were identified via linkage to state cancer registries. Those who reported cancer at the time of enrollment (n = 1,075) or were missing information about dicamba (n = 6,362); or missing information about covariates (n = 6,608) were excluded from the analysis. Females were excluded from the analysis because there were only four cancer cases among female participants. Pesticide exposure was assessed using responses about pesticide exposure captured on the enrollment questionnaires. Poisson regression was used to estimate individual RRs and 95% CIs, for the association between dicamba exposure and several cancers, adjusting for age, education, state of residence, smoking (pack years), family history of cancer, and total lifetime days of pesticide application. Lifetime exposure days were grouped into tertiles on the basis of

the distribution among all cancer cases combined and the highest tertile was divided at the median to create the following categories for lifetime exposure days for all cancer types: No exposure, 1 to < 20 days, 20 to < 56 days, 56 to < 116 days, and ≥ 116 days. For the intensity-weighted lifetime exposure days analysis, categories of exposure included no exposure, 1 to < 86.6, 86.6 to < 344.3, 344.3 to < 739.2, and ≥ 739.2 intensity-weighted days. Among the 41,969 male pesticide applicators included in the analysis, 22,036 (52.5%) reported exposure to dicamba. Of the 178 hematopoietic cancer cases included in the analysis, 96 reported exposure to dicamba. No evidence of a significant positive association was reported for any exposure level of lifetime days of dicamba use with the no exposed group or the low exposed group as the referent (0.69 < all RRs < 1.38; all 95% CIs encompassed the null value of 1.0; with n = 16 - 32 cases per exposure category; all p-trends > 0.05). No evidence of a significant positive association was reported for all exposure categories of intensity-weighted lifetime exposure days with the no exposed group and the low exposure group as the referent (0.83 < all RRs < 1.41; all 95% CIs encompassed the null value of 1.0; with n = 12 - 35 cases per exposure category; all p-trends > 0.05).

The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The ranking was based on the general strengths of the AHS, including its prospective design, ability to identify cancer cases through linkage to cancer registries, and exposure assessment approach which examined cumulative lifetime exposure to dicamba. Limitations were noted including the fact that the authors did not correct for/adjust for multiple comparison/multiple testing and that we would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and lymphohematopoietic cancers. One study, (Samanic et al., 2006), investigated the relationship between dicamba exposure and lymphohematopoietic cancers among pesticide applicators enrolled in the AHS prospective cohort and reported no evidence of a significant positive association, based on lifetime days and intensity-weighted lifetime days of use. The study quality was ranked moderate and several strengths were noted including the prospective cohort study design as part of the AHS, the ascertainment of cancer using established cancer registries, and the strengths of the AHS exposure assessment approach. The multiple comparisons performed without statistical correction for multiple comparisons was considered a limitation.

Leukemia

Three studies (Brown et al., 1990; Metayer et al., 2013; Lerro et al., 2020) assessed the association between exposure to dicamba and leukemias in adults and children.

- Brown et al. (1990) evaluated the association between several pesticides, including dicamba and leukemia among male farmers using data from concurrently conducted population-based case-control interview studies in Iowa and Minnesota between 1981-1984. Cases of leukemia were determined either by a tumor registry database or a special surveillance network including hospital and pathology records in Iowa and Minnesota. Eligibility criteria for cases included Caucasian males, aged ≥ 30 years old, who were diagnosed with leukemia both retrospectively (1 year prior to the start of the study) and prospectively (2 years following the start of the study). In Iowa, eligibility criteria were restricted to cases who were diagnosed between March 1981 and October 1983 and resided in any part of the state, and in Minnesota, a diagnosis period between October 1980 through September 1982 was required, with residence in cities besides Minneapolis, St. Paul, Rochester, or Duluth at the time of diagnosis. Pathology slides were used to ascertain cases by a group of trained pathologists.

Controls consisted of Caucasian males *not* diagnosed with hematopoietic or lymphatic cancer, who were part of a population-based sample, and frequency-matched to the cases based on vital status at the time of the interview, state of residence, and age group (within 5 years). Controls were identified through a separate population-based case-control for this study through a) random digit dialing; b) Medicare files; or c) state death certificates. An initial in-person interview was conducted by a trained professional for the cases and controls during August 1981 to March 1984, and information including study participant demographics, medical histories, occupational histories (both farming and nonfarming jobs), sources of drinking water, smoking and alcohol use, use of unpasteurized dairy products, and past farming practices was obtained via a standardized questionnaire at this time. For farming practices, detailed questions included the types of crop grown, and for specific pesticides, gathered information included the duration of pesticide use and if the respondent had personally mixed or applied the pesticide. Proxy respondents were used in place of the actual case or control due to death or incompetency during the interview portion of this study. During the initial interview, a total number of 578 cases were interviewed, with 340 of the cases living and 238 of the cases were deceased; for the controls (n = 1,245) 820 of the controls were living, and 425 were deceased. A second interview was carried out in 1987 via telephone to supplement the initial interview. Trained interviewers contacted study participants in Iowa to gather information concerning the usual number of days per year that each pesticide was used prior to and after 1960. For the supplemental interview, 86 of the 90 total cases completed the telephone interview (23 living, 63 deceased), and all 203 controls completed the interview (146 living, 57 deceased). Unconditional logistic regression was used to estimate the ORs and corresponding 95% CIs for the association between dicamba exposure and leukemia among male farmers, adjusting for state, age, tobacco use, high-risk occupations, vital status, family history of lymphopoietic cancer, and high-risk exposures. Among the 578 cases and 1,245 controls, 335 cases and 698 controls reported ever farming; the remaining cases and controls reported never farming (n = 243 cases, 547 controls). No evidence of a positive association was reported between dicamba ever use and leukemia among farmers, compared to nonfarmers (OR = 0.70; 95% CI: 0.40, 1.40; with n = 15 exposed cases and n = 57 exposed controls).

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths included the study design, frequency matching the cases to the controls, case ascertainment, and the in-person interviews. A main study limitation included the use of proxy respondents to collect pesticide exposure information for cases and controls. This was especially a concern during the supplemental interview, as the study reported that only 23 of the 86 respondents were living cases. This limitation likely contributed to information bias and led to exposure misclassification. Another study limitation included potential recall bias, as the cases living with the outcome may have remembered certain past exposures more accurately than the controls. As a result, this recall bias likely led to exposure misclassification as well. Finally, authors compared the farmers to nonfarmers, instead of exposed farmers to unexposed farmers, and any effects found from these comparisons might not be due to the chemical exposure but instead due to different risk of disease between two different subpopulations (farmers vs. nonfarmers).

- Metayer et al. (2013) evaluated the association between pesticide exposure within the home including dicamba and acute lymphoblastic leukemia (ALL) in children. Using data from the Northern California Childhood Leukemia Study, a population-based case-control study, cases included children ≤ 14 years of age who were diagnosed with ALL, enrolled in the Northern California Childhood Leukemia Study (NCCLS) during 1995 to 2008, and resided in one of the 35 pre-determined California counties within the San Francisco Bay area and California Central Valley. Cases were ascertained via pediatric clinical centers. Controls were randomly selected from state birth records and were frequency-matched to the cases via sex, ethnicity, date of birth, and mother's race. A total of 2,223 children (997 leukemia cases and 1226 healthy controls) including 882 case–control matched

sets, were enrolled in the NCCLS. From 2001 to 2007, NCCLS families with children <8 years of age and living in the same home occupied at the time of diagnosis for cases or reference date for controls were eligible to participate in a follow-up home visit to collect a dust sample and conduct a second interview. Pesticide exposure was assessed by measuring the concentration of pesticides including dicamba in a dust sample collected from a high volume surface sampler or the vacuum bag that collected dust from the location in the home where the child spent most of their time (as identified by parent). The dust samples were analyzed for select pesticides, including dicamba, using gas chromatography/mass spectrometry (dicamba detection limit of 1.05 ng/g) by laboratory staff who were blinded to case-control status. Among the 252 cases and 306 controls with dust samples, dicamba was detected in 60 (24%) samples from cases and 92 (30%) samples from controls. Authors reported that 5 (2%) samples from cases and 6 (2%) samples from controls were missing because of insufficient dust or interferences in the chemical analyses. Logistic regression was used to calculate ORs and 95% CIs for pesticide exposures including dicamba, controlling for the child's age, ethnicity, sex, household income, season of dust sampling, year of dust sampling, neighborhood type, residence type, and mother's race. Among the final number of cases (n = 252) and controls (n = 306), the analysis included 58 samples collected from households of cases and 92 samples collected from controls. No evidence of a positive association was reported for dicamba exposure and ALL (OR = 0.75; 95% CI: 0.50, 1.14).

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths included the study design, matching of the cases to the controls, case ascertainment, and the in-person interviews. Authors mentioned that case-control matched sets could not be maintained for participants who received a second interview and home visit to collect dust samples. While the study included individual-level assessment of exposure it was indirect and measurement of dicamba exposure through dust samples in the home occurred at a single timepoint approximately 1-2 years after diagnosis. Dust samples may be a poor surrogate for pesticide exposure.

- Lerro et al. (2020) investigated the association between dicamba exposure and several cancers including leukemia using data from the AHS prospective cohort. The study population (n = 49,992) consisted of pesticide applicators living in Iowa and North Carolina who were enrolled in the AHS cohort and who reported information on dicamba exposure at enrollment and follow-up. Incident cancer cases were identified using Iowa and North Carolina state cancer registry files from enrollment (1993-1997) through December 2014 in North Carolina and December 2015 in Iowa. International Classification of Diseases for Oncology (ICD-0-2) codes were used to classify cancer sites. Dicamba exposure was assessed through the enrollment questionnaire (1993 – 1997) and the first follow-up interview five years after enrollment (1999 – 2005). Multiple imputation was used to estimate pesticide exposures at follow-up for individuals who did not complete the interview (n = 20, 968, 37%). Poisson regression was used to calculate relative risks and 95% confidence intervals for each category of intensity-weighted days of dicamba use compared with no use, adjusting for age, race, sex, smoking, state, applicator type, education, imazethapyr use (Spearmen p = 0.49), and family history of cancer. Cumulative intensity-weighted days were categorized as no exposure or quartiles of intensity-weighted days of exposure among all incident cancer cases for sites with > 20 exposed (no use, 5.0 – 449.5 days, 449.6 – 1260.0 days, 1260.1 – 3,698 days, >3,689 days) or based on the median, as no, low or high exposure for cancers and subtypes with 10–20 exposed cases (no use, 5.0 – 1,260.0 days, > 1,260.0 days). Among the 49,922 applicators, 26,412 (52.9%) reported dicamba exposure and among the 136 cases of all leukemia combined, 76 reported dicamba exposure.

  No evidence of a significant positive association was reported for any exposure category for cumulative intensity-weighted days of dicamba exposure for *all leukemias combined*, and for the

subtypes of all *myeloid leukemias combined* and *chronic myeloid leukemia* (0.73 < all RRs < 1.31; all 95% CIs encompassed the null value of 1.0; with n = 7 – 21 cases per exposure category). For *acute myeloid leukemia*, a myeloid leukemia subtype, evidence of a positive association was reported in the middle exposure category for cumulative intensity-weighted days of dicamba exposure among a small number of cases (*>449.6–1260.0 days* – RR = 1.50; 95% CI: 1.04, 2.17; with n = 15 exposed cases). No evidence of a significant positive association was reported for the other exposure categories among a small number of cases (0.84 < RR < 1.17; all 95% CIs encompassed the null value of 1.0; with n = 9 - 11 cases per exposure category), with the no exposure group as the referent. Additionally, for *acute/other lymphocytic leukemia*, a subtype of leukemia, in the analysis of the association for cumulative intensity-weighted days of dicamba exposure, a moderately strong positive association was reported for the low exposure category and a strong positive association was reported for the high exposure category, among a very small number of exposed cases (*5.0 – 1,260.0 days* - RR = 2.60; 95% CI: 1.13, 5.96; with n = 3 exposed cases; *>1,260.0 days* – RR = 4.59; 95% CI: 2.11, 9.98; with n = 10 exposed cases; p-trend < 0.001).

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The general strengths of the publication included the underlying prospective design of AHS, focus on U.S. agricultural populations, and availability of a U.S. registry to comprehensively identify cancer cases. Lerro et al. (2020) indirectly assessed dicamba exposure based on the AHS survey instrument. Authors did not correct for multiple comparison/multiple testing and we would expect several statistically significant results to no longer be significant after such statistical adjustment. Results from the ever/never use analysis were not reported. We also note that the number of exposed cases per exposure category for several of the significant findings was very small (n ≤ 10) which makes the findings unreliable. Given the very small number of exposed cases and the multiple comparisons without correction, the reported estimates of associations between dicamba use and *acute myeloid leukemia* and *acute/other lymphocytic leukemia* were unreliable.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and leukemia among male farmers and children. Three studies (Brown et al., 1990; Metayer et al., 2013; Lerro et al., 2020) were identified that assessed the association between dicamba exposure and leukemia. Brown et al. (1990) reported no evidence of a positive association between dicamba and leukemia among adult males using data from population-based case-control interview studies in Minnesota and Iowa. The study quality was ranked moderate. Study limitations included the use of proxy respondents and recall bias which likely led to exposure misclassification and the comparison of two different subpopulations (farmers vs. nonfarmers) who have a different risk of disease. The second publication, Metayer et al. (2013), evaluated the association between childhood acute lymphoblastic leukemia (ALL) and pesticide exposure within the home in California. No evidence of a positive association was reported in children. Exposure to dicamba was assessed via in-person interviews and through dust samples collected from the home. The quality of the study was ranked moderate. Limitations included the indirect measurement of dicamba exposure through dust samples in the home which may be a poor surrogate for pesticide exposure (children likely spend several hours of the day at school) and exposure measurement occurred at a single timepoint approximately 1-2 years after diagnosis. And, a third publication, Lerro et al. (2020), reported no evidence of a significant positive association for any exposure category for cumulative intensity-weighted days of dicamba exposure for all leukemias combined among adults. When leukemia subtypes were examined separately, authors reported evidence of a positive association in the middle exposure category for cumulative intensity-weighted days of dicamba exposure and *acute myeloid leukemia*, and no evidence of a significant exposure-response trend among a small number of cases. And, for the subtype

Commented [JE8]: Confirm this is true for Brown 1990 and same as Cantor 1992 -nhl

acute/other lymphocytic leukemia, authors reported evidence of a moderately strong positive association for the low and a strong positive association for the high exposure categories, among a very small (<10) number of exposed cases and evidence of a significant exposure-response trend. However, these findings were reported among a small number of cases which makes the risk estimates unreliable. While the study benefited from the general strengths of the AHS prospective cohort, including study design, case ascertainment, and exposure assessment, authors performed multiple comparisons and did not correct for/adjust for the multiple comparisons/multiple testing. We would expect several statistically significant results to become not significant after such statistical adjustment. Results from the ever/never use analysis were not reported. We also note that the number of exposed cases was very small for several exposure categories which severely restricts our ability to interpret with confidence the observed effect estimates as well as the ability to assess the exposure-response relationship.

Hodgkin Lymphoma

Four studies (Pahwa et al., 2006; Karunanayake et al., 2012; Latifovic et al., 2020; Lerro et al., 2020) examined the association between dicamba exposure and Hodgkin Lymphoma (HL).

Commented [JE9]: •Kerunanake et al., 2012?

- Pahwa et al. (2006) investigated the potential association between pesticides, including dicamba and HL by conducting a population-based case-control study among men living in Canada known as the Cross-Canada Study of Pesticides and Health Study (CCSPH). The study population included males ≥ 19 years old, lived in one of six Canadian provinces and completed a postal questionnaire. Deceased participants were excluded from this analysis of the CCSPH data. Cases of HL included adult males diagnosed with HL between September 1991 to December 1994 and were ascertained via provincial cancer registries or hospital ascertainment (Quebec only). Cases were validated by a pathologist who reviewed pathology slides. Controls were randomly selected males from either health insurance records, telephone directories (Ontario) or voters lists (British Columbia), who resided in the same Canadian provinces as cases, and were matched to cases via age (± 2 years). A postal questionnaire was mailed to cases and controls to assess pesticide exposure, and follow-up telephone interviews regarding detailed pesticide use were conducted for each subject who reported more than 10 hours per year of pesticide use. The response rates for cases and controls was 67.1% and 48.0%, respectively.[20] Exposure to dicamba included pesticides with dicamba as the main active ingredient and mixtures of herbicides including dicamba as one of multiple active ingredients. Conditional logistic regression was used to calculate ORs and 95% CIs for dicamba and dicamba containing mixtures and HL, adjusting for age and province of residence. Among the total HL cases (n = 316), 32 reported exposure to any dicamba containing herbicide, and 131 of the 1,506 controls reported exposure to any dicamba containing herbicide. No evidence of a significant positive association was reported for any dicamba exposure (including mixtures)[21] and HL (OR = 1.30; 95% CI: 0.82, 2.04; with n = 32 exposed cases and n = 131 exposed controls). A sub-analysis conducted to determine if co-exposures to DEET and dicamba affected the odds of HL among participants reported no evidence of a positive association relative to exposure to DEET and dicamba (OR = 0.96; 95% CI: 0.54, 1.71), respectively. And finally, in an additional analysis that was limited to farm workers/dwellers only, similarly reported no evidence of a significant positive association between exposure to dicamba-containing

[20] McDuffie, H. H., Pahwa, P., Robson, D., Dosman, J. A., Fincham, S., Spinelli, J. J., & McLaughlin, J. R. (2005). Insect repellents, phenoxyherbicide exposure, and non-Hodgkin's lymphoma. J Occup Environ Med, 47(8), 806-816. doi:10.1097/01.jom.0000167260.80687.78

[21] For any dicamba exposure, authors included exposures to dicamba as the sole active ingredient and to products that were mixtures that contained active ingredients in addition to dicamba such as: dicamba and glyphosate; and dicamba, 2,4-D, and mecoprop.

herbicides and HL (OR = 1.28; 95% CI: 0.68, 2.39 with n = 21 exposed cases, n = 97 exposed controls).

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths included the study design, age matching the cases to the controls, and case ascertainment. Additionally, authors conducted a pilot study prior and a validation exercise for the study questionnaire as means to assess exposure accurately. Study limitations were related to the case-control study design and consisted of the potential for selection bias and recall bias. Another study limitation included potential recall bias, as the cases living with the outcome may have remembered certain past exposures more accurately than the controls. As a result, this recall bias may have led to exposure misclassification as well. Another limitation of the study was the low response rate to the mailed questionnaires. Only 67.1% of the contacted cases and 48% of the contacted controls responded to the questionnaire and were included in the analysis. There may have been differences between those who responded and those who did not respond.

- Karunanayake et al. (2012) further investigated the association between pesticide exposures, including dicamba, and HL among the CCSPH cohort, that considered medical history in the analysis. As above in Pahwa et al. (2006), the study population included males ≥19 years old, lived in one of six Canadian provinces and completed a postal questionnaire. Deceased participants were excluded from this analysis of the CCSPH data. Cases of HL included adult males diagnosed with HL between September 1991 to December 1994 and were ascertained via provincial cancer registries or hospital ascertainment (Quebec only). Cases were validated by a pathologist who reviewed pathology slides. Controls were randomly selected males from either health insurance records, telephone directories (Ontario) or voters lists (British Columbia), who resided in the same Canadian provinces as cases, and were matched to cases via age (± 2 years). A postal questionnaire was mailed to cases and controls to assess pesticide exposure, and follow-up telephone interviews regarding detailed pesticide use were conducted for each subject who reported more than 10 hours per year of pesticide use. The response rates for cases and controls was 67.1% and 48.0%, respectively.[22] Exposure to dicamba included pesticides with dicamba as the main active ingredient and mixtures of herbicides including dicamba as one of multiple active ingredients. Conditional logistic regression was used to calculate ORs and 95% CIs for dicamba and dicamba containing mixtures and HL, adjusting for age and province of residence. Among the total HL cases (n = 316), 32 reported exposure to any dicamba containing herbicide, and 131 of the 1,506 controls reported exposure to any dicamba containing herbicide. No evidence of a significant positive association was reported for any dicamba exposure (including mixtures)[23] and HL (OR = 1.29; 95% CI: 0.82, 2.04; with n = 32 exposed cases and n = 131 exposed controls). In an additional analysis, that further adjusted for medical variables that were statistically significant in bivariable analysis ($p < 0.20$), including history of measles, acne, hay fever, shingles, and a positive family history (1st degree relative) of cancer no evidence of a significant positive association was reported (OR = 1.16; 95% CI: 0.71, 1.90). In the same two analysis for individual dicamba herbicides (Banvel, Target), no evidence of a significant positive association was reported for the association between dicamba exposure and HL, adjusted for age group and province of residence (OR = 1.25; 95% CI: 0.61, 2.55; with n = 12 exposed cases and n = 50 exposed controls). And, no evidence of a positive association was reported for the association between dicamba and HL, when further adjusted for history of measles, acne, hay fever, shingles, and a positive family history

[22] McDuffie, H. H., Pahwa, P., Robson, D., Dosman, J. A., Fincham, S., Spinelli, J. J., & McLaughlin, J. R. (2005). Insect repellents, phenoxyherbicide exposure, and non-Hodgkin's lymphoma. J Occup Environ Med, 47(8), 806-816. doi:10.1097/01.jom.0000167260.80687.78

[23] For any dicamba exposure, authors included exposures to dicamba as the sole active ingredient and to products that were mixtures that contained active ingredients in addition to dicamba such as: dicamba and glyphosate; and dicamba, 2,4-D, and mecoprop.

(1st degree relative) of cancer (OR = 0.96; 95% CI: 0.43, 2.15; with n = 12 exposed cases and n = 131 exposed controls).

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths included the study design, age matching the cases to the controls, and case ascertainment. Additionally, authors conducted a pilot study prior and a validation exercise for the study questionnaire as means to assess exposure accurately. Study limitations were related to the case-control study design and consisted of the potential for selection bias and recall bias. Another study limitation included potential recall bias, as the cases living with the outcome may have remembered certain past exposures more accurately than the controls. As a result, this recall bias may have led to exposure misclassification as well. Another limitation of the study was the low response rate to the mailed questionnaires. Only 67.1% of the contacted cases and 48% of the contacted controls responded to the questionnaire and were included in the analysis. There may have been differences between those who responded and those who did not respond.

- Latifovic et al. (2020) investigated the association between exposure to pesticides including dicamba the risk of HL among male farmers in the United States and Canada. The study population in the pooled analysis (HL = 507, Controls = 3,886) included participants enrolled in three of the four case-control studies that compose the North American Pooled Project (NAPP) in Nebraska, Kansas, and six Canadian provinces.[24] Cases of HL (n = 507) were identified through the state cancer registry (Kansas, enrolled 1976 - 1982) and special surveillance of hospital and pathology records or study groups (Nebraska, enrolled 1983 - 1986) and cancer registries of the six Canadian provinces and hospital ascertainment in Quebec (enrolled 1991 – 1994). Population-based controls (n = 3,886) were selected through random digit dialing, Medicare, or from state mortality records (deceased controls), provincial health insurance records, telephone listings, and voter's lists. Within each study, there were differences in matching of controls to cases including: age (± 2 years) and vital status in Kansas; frequency-matched 3:1 by race, age (± 2 years) sex, and vital status in Nebraska; and, cases and controls were stratified by age (± 2 years) and province in Canada. Controls were matched to the age groupings of all cancer cases recruited by the NAPP and not specifically to HL cases. Pesticide exposure was assessed using questionnaires administered via telephone in Kansas and Nebraska and from a mailed questionnaire to all participants and a follow-up telephone interview for those who reported ≥ 10 hours per year of pesticide use in Canada. Participants in Canada and Nebraska received a list of chemicals and trade names for their questionnaires, participants in Kansas did not. Questionnaires also collected demographic, lifestyle, and occupational characteristics, and cancer risk factors including medical history. To validate pesticide use Kansas and Canada compared a subset of respondents self-reported pesticide use to pesticide suppliers' records of purchase and 60% agreement was reported in Kansas and agreement in Canada was reported as excellent. In Nebraska and Kansas response rates for the study populations ranged from 69.9% - 94% (response rates for HL in Canada were not reported) and proxy respondents were used for those unable to complete questionnaires in Kansas and Nebraska (Cases: 22.9 % - 26.5%; Controls: 43.6% - 52.3%). Logistic regression was used to estimate ORs and 95% CIs for the association between dicamba exposure and HL, adjusted

[24] Three population-based case-control studies included in the Latifovic et al. (2020) analysis:
1. Hoar SK, Blair A, Holmes FF, Boysen CD, Robel RJ, Hoover R, Fraumeni JF Jr (1986) Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA 256(9):1141–1147
2. Zahm SH, Weisenburger DD, Babbitt PA, Saal RC, Vaught JB, Cantor KP, Blair A (1990) A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4D) in eastern Nebraska. Epidemiology 1(5):349–356
3. McDuffie HH, Pahwa P, McLaughlin JR, Spinelli JJ, Fincham S, Dosman JA, Robson D, Skinnider LF, Choi NW (2001) NonHodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. Cancer Epidemiol Biomarkers Prev 10(11):1155–1163

for age, state or province of residence, and respondent type (self, proxy). Covariates were selected using theoretical consideration of the relationships determined using the directed acyclic graph approach and a change in estimate method (10% change in the coefficient estimate) was used to create the final model. Study participants missing covariate data were excluded from the analysis, leaving 496 cases and 3,789 controls. No evidence of a significant positive association was reported between dicamba exposure and HL among a small number of cases (OR = 1.28; 95% CI 0.71, 2.30; with n = 16 exposed cases and n = 86 exposed controls), based on ever use. And similarly, no evidence of a significant positive association was reported when stratified by age (≤ 40 years – OR = 2.09; 95% CI: 0.91, 4.81; with n = 12 exposed cases; > *40 years* – OR: 0.71; 95% CI: 0.25, 1.99; with n = 4 exposed cases).

The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths include the case-control study design, and validation of HL diagnosis. Recall bias was a potential study limitation, as the cases living with the outcome may have remembered certain past exposures more accurately than the controls and this may have contributed to exposure misclassification as well. Case and control selection methods differed between each study which likely led to selection bias, and different methods were used to collect pesticide use information (postal vs. telephone) potentially causing some misclassification of exposure. Certain participants who were prompted with a list of pesticide names may have remembered their pesticide exposures more accurately than those who were not prompted with pesticide names. Additionally, a large percentage of proxy respondents was reported by the study authors (~31%) which could have contributed to information bias and led to exposure misclassification; however, we note the study authors performed sensitivity analysis with proxy respondents excluded and reported that results were qualitatively similar. Lastly, we note that even though the overall study population was large, a small number of cases were reported HL.

- Lerro et al. (2020) investigated the association between dicamba exposure and cancers including HL using data from the AHS prospective cohort. The study population (n = 49,992) consisted of pesticide applicators living in Iowa and North Carolina who were enrolled in the AHS cohort and who reported information on dicamba exposure at enrollment and follow-up and is described in greater detail in the Cancer (all sites) section above. Briefly, incident cancer cases were identified from enrollment (1993-1997) through December 2015 and dicamba exposure was assessed through the enrollment and 5-year follow-up interview questionnaires. Poisson regression was used to calculate relative risks and 95% confidence intervals for each category of intensity-weighted days of dicamba use compared with no use, adjusting for age, race, sex, smoking, state, applicator type, education, imazethapyr use (Spearmen p = 0.49), and family history of cancer. Among the 49,922 applicators, 26,412 (52.9%) reported dicamba exposure and among the 27 HL cases, 13 reported dicamba exposure. No evidence of a significant positive association was reported for any exposure category of dicamba intensity-weighted lifetime days of exposure and HL among pesticide applicators in the AHS (0.50 < RR < 1.06; all 95% CIs encompassed the null value of 1.0; with n = 4 – 9 exposed cases per exposure category), with the no exposure group as the referent.

  The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The general strengths the prospective design of AHS, focus on U.S. agricultural populations, and availability of a U.S. registry to comprehensively identify cancer cases and the exposure assessment. We note that authors did not correct for/adjust for multiple comparison/multiple testing and we would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and HL. Three studies (Pahwa et al., 2006; Karunanayake et al. (2012); Latifovic et al., 2020; Lerro et al., 2020) were identified that assessed the association between dicamba exposure and HL. Pahwa et al. (2006) reported no evidence of a significant positive association between dicamba and HL in a population-based case-control study among men living in Canada as part of the Cross-Canada Study of Pesticides and Health Study (CCSPH). The age matched cases and controls, case ascertainment, and the validation of the exposure questionnaire were considered strengths. Study limitations were related to the case-control study design and consisted of the potential for selection bias and recall bias and low response rate. The study was ranked moderate quality. A second study, Karunanayake et al. (2012), that also examined the association among the CCSPH cohort, additionally adjusted for history of measles, acne, hay fever, shingles, and a positive family history (1st degree relative) of cancer, reported no evidence of a significant positive association between exposure to mixtures of pesticides containing dicamba and HL and no evidence of a positive association between exposure to pesticides containing dicamba as the only active ingredient and HL. A third study, Latifovic et al. (2020), reported no evidence of a significant positive association between dicamba ever use and HL among a small number of cases in a pooled analysis of three case-control studies in Nebraska, Kansas, and six Canadian provinces. This study quality was ranked moderate. Limitations included potential recall bias due to cases potentially remembering exposure differently than controls, different selection methods used for cases and controls, and different exposure assessments across studies. And a fourth study, Lerro et al., (2020) reported no evidence of a significant positive association for any exposure category of dicamba intensity-weighted lifetime days of exposure among the AHS prospective cohort of pesticide applicators and was ranked moderate quality. Authors did not correct for multiple comparison and this was considered a limitation as several significant findings would likely no longer be significant after statistical correction for multiple comparisons. Additionally, results from the ever/never use analysis were not reported.

Non-Hodgkin Lymphoma

Nine publications (Cantor et al., 1992; McDuffie et al., 2001; McDuffie et al., 2005; De Roos et al., 2003; Hartge et al., 2005; Samanic et al., 2006; Czarnota et al., 2015; Leon et al., 2019; Lerro et al., 2020) were identified that assessed exposure to dicamba and non-Hodgkin lymphoma (NHL).

- Cantor et al. (1992) investigated the association between dicamba exposure and NHL among male farmers in Iowa and Minnesota. Using data from two population-based case-control studies, cases were determined either by the state health registry database or a special surveillance network including hospital and pathology records in Iowa and Minnesota. Eligibility criteria for cases included males, aged ≥ 30 years old, who were recently diagnosed with NHL. In Iowa, eligibility criteria were restricted to cases who were diagnosed between March 1981 and October 1983 and resided in any part of the state, and in Minnesota, a diagnosis period between October 1980 through September 1982 was required, with residence in cities besides Minneapolis, St. Paul, Rochester, or Duluth at the time of diagnosis. NHL cases were confirmed by four pathologists by morphology, and the NHL subtype was determined when three of the four pathologists were in agreement with the subtype during the histopathologic review;[25] the subtypes included follicular, diffuse, small lymphocytic, and "other" NHL. Controls consisted of Caucasian white males, who had *not* been diagnosed with hematopoietic or lymphatic cancer and were randomly selected and frequency-matched to the cases based on vital

[25] The study mentioned that cases were considered "unclassifiable" if the panel of pathologists (three of the four) were not in agreement with the specific subtype of NHL, or if a specific subtype could not be determined from the provided tissue sample.

status at the time of the interview, state of residence, and age group (within 5 years). Controls were identified through a separate population-based case-control for this study through a) random digit dialing; b) Medicare files; or c) state death certificates. In-person interviews were conducted by a trained professional for the cases and controls during August 1981 to March 1984, to obtain information about study participant demographics, medical history, occupational history (both farming and nonfarming jobs), past farming practices and pesticide exposures (type and duration of use, and application method). Non-farmers (those who had never lived or worked on a farm as an adult) served as the reference population. Of the 622 cases interviewed, 184 (30%) of the cases were interviewed via proxy due to death or incompetency and, of the 1,245 controls, 425 (34%) controls were interviewed via surrogate. Unconditional logistic regression was conducted to determine ORs and corresponding 95% CIs for the association between dicamba exposure and NHL among male farmers, adjusting for age, state, cigarette smoking status, high-risk occupations (e.g., nonfarming job related to NHL in this study), family history of lymphopoietic cancer, and high-risk exposures (e.g., exposure to hair dyes). For NHL subtypes, polychotomous logistic models were run using software created by the National Cancer Institute. Among the total cases (n = 622), the following cases of NHL subtypes were reported: 198 (31.8%) diffuse, 195 (31.4%) follicular, 85 (13.7%) small lymphocytic cell, and 144 (23.2%) other and undefined lymphomas. When the NHL cases and controls were further stratified by occupation, specifically farming, 356 of the 622 total cases (57%) and 698 of the total 1,245 controls) reported ever farming; the remaining cases and controls reported never farming (n = 266 cases, 547 controls). No evidence of a significant positive association was reported between dicamba exposure and NHL among farmers based on ever/never use (OR: 1.20; 95% CI: 0.70, 2.00 with n = 28 cases, 57 controls). Additionally, when dicamba exposure was limited to pesticide use prior to 1965 (chosen because 15-18 years prior to diagnosis was a reasonable minimal latency period), an elevated but not significant positive association was reported for dicamba use before 1965 and NHL among a very small number ($n \leq 10$) of cases (OR: 2.80; 95% CI: 0.96, 8.10 with n = 7 exposed cases, n = 7 exposed controls). Additionally, no evidence of a significant positive association was reported between dicamba and NHL when dicamba was handled without protective equipment, (OR: 1.40; 95% CI: 0.80, 2.50 with n = 19 cases, 32 controls). And finally, when state of residence among participants was considered, an elevated but not significant positive association was reported among a very small number of cases in *Minnesota* (OR = 3.9; 95% CI: 0.60, 24.0, with n = 3 exposed cases and n = 2 exposed controls) and no evidence of a significant positive association was reported for dicamba exposure and NHL among a very small number of cases in Iowa (OR = 2.10; 95% CI: 0.60, 8.10, with n = 4 exposed cases and n = 5 exposed controls). We note the OR for Minnesota was elevated (OR >2.5) however the very small (<10) number of exposed cases makes the odds ratio unreliable.

Commented [JE10]: Conditional for age-matched case-control studies. Something in study design that makes conditional inappropriate?

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths included the study design, frequency matching the cases to the controls, the adequate statistical methods, the measures taken to ascertain the study cases, and the in-person interviews conducted. A main study limitation included the use of proxy respondents among the cases and controls during the exposure assessment. The study indicated that 30% and 34% of the total cases and controls used proxy respondents to report their exposure, which may have contributed to information bias and led to exposure misclassification. Another study limitation included potential recall bias, as the cases living with the outcome may have remembered certain past exposures more accurately than the controls. As a result, this recall bias may have led to exposure misclassification as well. Another limitation of the study is that it appears the authors compared the odds of cases of exposed farmers to nonfarmers, instead of exposed farmers to unexposed farmers, and any effects found from these comparisons might not be due to the chemical exposure but instead due to different risk of disease between two different subpopulations (farmers vs. nonfarmers). Another study limitation included the fact that case and control selection methods differed between each study and

likely led to selection bias, and different methods were used to collect pesticide use information (list of pesticides vs. voluntary recall). We also note the very small number of dicamba-exposed cases which severely restricts the interpretability of the odds ratios between dicamba exposure and NHL.

- In another study, McDuffie et al. (2001) evaluated the potential association between pesticides, including dicamba and NHL by conducting a population-based case-control study among men living in Canada, known as the Cross-Canada Study of Pesticides and Health Study (CCSPH). Incident NHL cases included males who were: ≥ 19 years of age, diagnosed with NHL between September 1991 to December 1994, who resided in either Quebec, Ontario, Alberta, Saskatchewan, Manitoba, or British Columbia. Cases were ascertained using cancer registries or hospital ascertainment (Quebec only), and pathology slides were reviewed by pathologists for validation. Authors reported that 84 % (436 of 517) of the NHL tumors were validated. Controls were randomly selected males from either health insurance records, telephone directories (Ontario) or voters lists (British Columbia), who resided in the same Canadian provinces, and were matched to the cases via age (± 2 years). A postal questionnaire was mailed to the confirmed cases to assess pesticide exposure, and follow-up telephone interviews regarding detailed pesticide use were conducted for each subject who reported more than 10 hours/year of pesticide use. The response rates for the cases and controls was 67.1% and 48.0%, respectively. A conditional logistic regression was used to calculate ORs and 95% CIs for individual pesticide exposures including dicamba, adjusting for age and province of residence. Among the total NHL cases (n = 517), 73 reported exposure to dicamba, and 131 of the 1,506 controls reported dicamba exposure. Evidence of a positive association was reported for any dicamba exposure (including mixtures)[26] when the model was adjusted for age and province of residence (OR = 1.68; 95% CI: 1.00, 2.81; with n = 26 exposed cases and n = 31 exposed controls), and when the model was further adjusted for additional medical variables[27] (OR = 1.88; 95% CI: 1.32, 2.68; with n = 73 exposed cases and n = 131 exposed controls). However, when dicamba exposure was limited to products with dicamba as the only active ingredient, no evidence of a significant positive association was reported for either model (adjustment for age and province – OR = 1.59; 95% CI: 0.95, 2.63; adjusted for age, province and medical variables – OR = 1.68; 95% CI: 1.00, 2.81; with n = 26 exposed cases and n = 31 exposed controls). In an additional analysis that analyzed frequency of exposure to dicamba (as an individual compound) that divided days per year of exposure into two categories of lifetime exposure (no exposure vs. ≥ 1 day per year of exposure), no evidence of a significant positive association was reported for ≥ 1 day per year of dicamba exposure and NHL (OR = 1.58; 95% CI: 0.96, 2.62; with n = 26 exposed cases and n = 50 exposed controls), with the no exposure group as the referent.

  The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths included the study design, age matching the cases to the controls, the adequate statistical methods, and the measures taken to ascertain the study cases. A main study limitation included the use of proxy respondents among the cases and controls during the exposure assessment even though authors attempted to minimize the number of proxy respondents by making deceased ineligible to participate. Authors did not specify the percentage of the total cases and controls that used proxy respondents to report their exposure. Use of proxy respondents may have contributed to information bias and led to exposure misclassification. Another study limitation included potential recall bias, as the cases living with the outcome may have remembered certain past exposures more accurately than the controls. As a result, this recall bias may have led to exposure

[26] For any dicamba exposure, authors included exposures to dicamba as the sole active ingredient and to products that were mixtures that contained active ingredients in addition to dicamba such as: dicamba and glyphosate; and dicamba, 2,4-D, and mecoprop.
[27] Medical variables included the following: history of measles, mumps, cancer, allergy, desensitization shots, and a positive family history of cancer in a first-degree relative).

misclassification as well. Another limitation of the study was the response rate. Only 67.1% of the contacted cases and 48% of the contacted controls responded to the mailed questionnaire and were included in the analysis. There may have been differences between those who responded and those who did not respond.

- In an extended analysis of McDuffie et al. (2001), McDuffie et al. (2005) examined the effect of using rubber gloves and handling the insect repellent, DEET on the association between pesticide exposure including dicamba and NHL. Using data from the Cross-Canada Study of Pesticides and Health Study (CCSPH), and methods as described in McDuffie et al. (2001) above, a conditional logistic regression was used to calculate ORs and 95% CIs for individual pesticide exposures including dicamba, controlling for age and province of residence. Among the 513 NHL cases, 71 reported exposure to dicamba (52 exposed to both DEET and dicamba, 19 exposed to dicamba but not DEET), and among the 1,506 controls, 128 reported dicamba exposure (93 exposed to both DEET and dicamba, 38 exposed to dicamba but not DEET). In an analysis that investigated the association between co-exposure to dicamba and DEET and NHL, evidence of a positive association was reported between dicamba and DEET co-exposure and NHL (OR = 1.84; 95% CI: 1.23, 2.75; with n = 52 exposed cases and n = 93 exposed controls). However, no evidence of a significant positive association was reported between dicamba and NHL when there was no DEET exposure (OR = 1.39; 95% CI: 0.77, 2.50; with n = 19 exposed cases and n = 38 exposed controls).

  In an additional sub-analysis of the study population that was comprised of farm dwellers/workers only (n = 235 total cases and 673 controls) evidence of a positive association was reported between exposure to dicamba containing herbicides (including mixtures) and NHL, when participants also reported exposure to DEET and use of rubber gloves (OR = 2.04; 95% CI: 1.02, 4.06 with n = 18 exposed cases and n = 40 exposed controls) with no exposed group as the referent (no exposure to DEET, nor to dicamba containing herbicide, nor use of rubber gloves). However, no evidence of a significant positive association was reported between exposure to dicamba containing herbicides (including mixtures) and NHL, when participants also reported exposure to either DEET or use of rubber gloves or reported no exposure to either DEET or rubber gloves in a combined analysis (OR = 1.58; 95% CI: 0.90, 2.76 with n = 28 exposed cases and n = 57 exposed controls) with no exposed group as the referent (no exposure to DEET, nor to dicamba containing herbicide, nor use of rubber gloves).

  The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths included the study design, age matching the cases to the controls, the adequate statistical methods, and the measures taken to ascertain the study cases. A main study limitation included the use of proxy respondents among the cases and controls during the exposure assessment even though authors attempted to minimize the number of proxy respondents by making deceased ineligible to participate. Authors did not specify the percentage of the total cases and controls that used proxy respondents to report their exposure. Use of proxy respondents may have contributed to information bias and led to exposure misclassification. Another study limitation included potential recall bias, as the cases living with the outcome may have remembered certain past exposures more accurately than the controls. As a result, this recall bias may have led to exposure misclassification as well. Another limitation of the study was the response rate to the mailed questionnaires. Only 67.1% of the contacted cases and 48% of the contacted controls responded to the questionnaire and were included in the analysis. There may have been differences between those who responded and those who did not respond.

- De Roos et al. (2003) investigated the association of NHL and specific pesticides including dicamba, using a pooled analysis of three case-control studies (Cantor et al., 1992; Hoar et al., 1986; Zahm et

al., 1990). These three studies were performed by the National Cancer Institute to evaluate pesticide exposures and NHL in four Midwestern states within the United States, Iowa, Nebraska, Kansas, and Minnesota. The recruitment phase of each study differed. For Nebraska, cases were defined as Caucasian male subjects, diagnosed with NHL between July 1983 and June 1986, who lived in eastern Nebraska (one of the 66 counties) and were aged ≥ 21 years old.[28] Cases in Nebraska were identified through the Nebraska Lymphoma Study Group and local hospitals. In Kansas, cases were randomly selected from the state cancer registry, were Caucasian male subjects, diagnosed with NHL during 1979 and 1981, and were aged ≥ 21 years old.[29] In Minnesota and Iowa, cases were recently diagnosed with NHL, Caucasian male subjects, and aged ≥ 30 years old.[30] These cases were ascertained using records from the state cancer registry between 1981 to 1983 in Iowa, and from a surveillance program in hospitals and pathology laboratories in Minnesota during 1980 to 1982. Controls were randomly selected from a population of people living within a similar geographic location as the cases through Medicare records, random digit dialing, and state mortality files (deceased only). Also, the controls were frequency-matched to cases through race, sex, age and vital status. Pesticide exposure was assessed through questionnaires administered by interviewers to study participants or proxy respondents (if respondents were deceased or incapacitated), using a series of exposure-related questions asked in various ways (e.g., directly vs. open-ended questions) depending on the state. A logistic regression and a hierarchical regression were used to calculate odds ratios and 95% confidence intervals for individual pesticide exposures, and each was adjusted for all of the other 46 pesticides assessed in this study, age, and study location. Among the total number of cases (n = 870) and controls (n = 2,569), 545 (62.6%) of the cases self-reported exposure and 325 (37.4%) exposure was reported via proxy respondent. For the controls, 1,413 (55.0%) self-reported exposure and 1,156 (45.0%) reported exposure via proxy respondent. When missing data variables were excluded from the analyses, 39 (6.0%) of 650 cases and 79 (4.10%) of 1,933 controls reported dicamba exposure. No evidence of a significant positive association was reported between dicamba exposure and NHL for both the logistic and hierarchical regressions (OR = 1.20; 95% CI: 0.60, 2.30; OR = 1.20; 95% CI: 0.70, 2.10), respectively.

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The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The pooled study design enabled the investigators to combine data from three population-based case-control studies which increased the number of exposed subjects and made it possible to include assessment of dicamba, even though dicamba use was relatively rare in both cases and controls (6.0% and 4.1% of cases and controls, respectively). Another strength of the study was that all cases were identified through established cancer registries and were clinically confirmed. With regard to limitations, recall bias was likely if the cases were more likely to recall past pesticide use than control subjects. The use of proxy respondents (up to 37% of cases and 45% of controls) to capture pesticide use information was considered a study limitation as recall by proxy respondents may not be as accurate as from the actual pesticide user. Authors reported higher ORs for proxy respondents than for direct respondents. Additionally, the case selection methods differed between each study which likely led to selection bias and different methods used to collect pesticide use information between studies potentially led to misclassification of exposure. Certain participants who were prompted with a list of pesticide names may have remembered their pesticide exposures more accurately than those who were not prompted with pesticide names.

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[28] Zahm SH, Weisenburger DD, Babbitt PA, et al. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. Epidemiology 1990; 1:349–56.

[29] Hoar SK, Blair A, Holmes FF, et al. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA,1986;256:1141–7.

[30] Cantor KP, Blair A, Everett G, et al. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. Cancer Res 1992; 52:2447–55.

- Hartge et al. (2005) investigated the potential association between dicamba exposure and other pesticides and NHL in a population-based case-control study in the United States. Using data from the Surveillance Epidemiology and End Results (SEER) cancer registries, cases included adults ≥ 20 – 74 years old, diagnosed with NHL during 1998 to 2000, who lived in one of the four areas Los Angeles, Detroit, Seattle, or Iowa. Controls were selected via random digit dialing (for those aged 20 – 64 years old) or through Medicare records. Pesticide exposure including dicamba was assessed through in-home interviews for study participants who lived at their residence for at least 2 years since 1970. During the home visit, vacuum cleaner bags were collected to detect pesticides in carpet dust from a subset of residents who used their vacuum cleaner in the past year and owned at least half of their carpets for ≥ 5 years. Gas chromatography/ mass spectrometry was used to detect dicamba along with four other herbicides in the carpet dust samples (dicamba detection limit: 85.3 ng/g). Logistic regression was used to calculate RRs and 95% CIs for pesticide exposures including dicamba, adjusted for age, residence, sex, education, and race. Among the 1,728 cases and 2,046 controls for whom interviews were attempted, 1,321 cases and 1,057 controls completed the in person interviews and the final data set included 679 cases and 510 controls with carpet dust samples. Authors reported that detection of dicamba in carpet dust samples correlated very well with self-reported usage patterns. No evidence of a positive association was reported for the association between dicamba exposure and NHL among respondents reporting ≥ 50 applications with levels of dicamba at or above 500 ng/g in carpet dust samples (RR = 0.85; 95% CI: 0.20, 3.62, the number of exposed cases and controls not reported) when compared to those who reported no herbicide exposure and no dicamba was detected in their carpet dust samples (187 cases and 146 controls). In an exposure-response analysis using dicamba levels detected in carpet dust samples to estimate dicamba exposure, the following quartiles of exposure were constructed: below the detection limit (85.3 ng/g), <500 ng/g, 500 – 999 ng/g, and < 1,000 ng/g. RRs were calculated for each quartile, with *below the detection limit* as the referent. No evidence of a significant positive association was reported for the association between dicamba exposure at any level of detection in carpet dust samples and NHL (0.63 > all RRs > 1.16; all 95% CIs encompassed the null value 1.0; with n = 6 – 84 exposed cases per exposure category). Although a p-trend was not reported, there appeared to be no evidence of an exposure-response trend on visual inspection.

  The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths included the use of the SEER cancer registry to identify cases, and the reported exposure correlated with detected exposure in carpet dust samples. Limitations included potential recall bias due to cases potentially remembering exposure differently than controls and different selection methods used for cases and controls.

- Czarnota et al. (2015) investigated the association between pesticide exposure, including dicamba, and NHL in a population-based case control study at four NCI SEER study sites in the United States. The study population included participants living in Iowa, Los Angeles, California, Seattle, Washing and Detroit, Michigan. Cases included those aged 20 – 74 years with a primary diagnosis of NHL between July 1998 and June 2000, living in one of the four study areas. Those cases who were no longer living, who had HIV, or whose physician refused to participate were ineligible for the study. Of the 1,728 eligible cases that were contacted, 1,321 (76%) participated. Controls included participants selected from either Center for Medicare and Medicaid Services files (≥65 years old) or from the general population using random digit dialing (<65 years old). Controls were frequency matched to cases by age (± 5 years), sex, race, and study site. Of the 2,046 eligible controls contacted to participate, 1,057 (52%) participated in the study. Pesticide exposure was assessed using dust samples collected from vacuum cleaners between February 1999 and May 2001. Dust samples were collected from consenting participant's vacuum cleaners if the vacuum was used in the past year and if participants owned at least half of their rugs for five or more years. Of the samples collected from

695 cases and 521 controls, 682 (98%) samples from cases and 513 (98%) of controls were successfully analyzed between September 1999 and September 2001. Authors noted a change in analytic procedures during the study resulted in increased detection limits for methoxychlor from 20.7 to 62/5 ng/g). The detection limit for dicamba was 42-84 ng/g. Chemical concentrations were assumed to follow a log-normal distribution and missing values were imputed to create 10 complete data sets for dicamba and the other 26 analytes. Quartiles of exposure were created based on study site specific cut points based on the distribution of cases and controls combined. Nonlinear logistic regression was used to determine ORs and 95% CIs for the association between exposure to individual pesticides, including dicamba, and NHL, adjusted for age, race, sex and education level. The OR for three highest quartiles were compared to the first quartile of exposure was reported for dicamba. Additionally, authors analyzed the association between exposure to a mixture of 27 chemicals and NHL. As this is not the focus in this memo do not present the results for the mixture analysis. In the analysis of the association between dicamba exposure and NHL among all study sites combined, no evidence of a positive association was reported (OR = 0.74; 95% CI: 0.53, 1.04). Similarly, no evidence of a positive association was reported for three of the four study sites when considered separately (*Iowa* – OR = 0.48; 95% CI: 0.26, 0.90; p-value = 0.02; *Seattle* – OR = 0.41; 95% CI: 0.22, 0.76; p-value < 0.01; *Los Angeles* – OR = 0.93; 95% CI: 0.48, 1.81; p-value > 0.05). And for the analysis using data from the forth study site, Detroit, no evidence of a significant positive association was reported for the association between dicamba and NHL when the top three exposure quartiles were compared to the lowest exposure category (OR = 1.07; 95% CI: 0.45, 2.54; p-value > 0.05). Authors did not report the number of cases that reported dicamba exposure (overall or by study site).

Commented [JE12]: may need to reference other study to fully describe this.

The study quality was ranked moderate quality based on the study quality criteria provided in the OPP Framework. The ability to identify cancer cases through linkage to cancer registries and a matched case control analysis were strengths. However, the exposure assessment approach which examined ever exposure to dicamba through dust samples collected from in the home a few years after cancer diagnosis was a limitation. Additionally, as pointed out by authors, the single chemical analysis, did not take into account confounding by other chemicals. Finally, the number of cases and controls with dicamba exposure were not reported but would have been helpful in assessing the effect measures.

- Samanic et al., 2006 examined the association between dicamba exposure and several cancers, including NHL among pesticide applicators in the AHS prospective cohort. The study population included male pesticide applicators living in Iowa and North Carolina who completed the AHS enrollment questionnaires and had complete data on dicamba and covariates. Cases of incident cancer (first primary cancer) diagnosed between enrollment (1993 - 1997) and December 31, 2002 were identified via linkage to state cancer registries. Those who reported cancer at the time of enrollment (n = 1,075) or were missing information about dicamba (n = 6,362); or missing information about covariates (n = 6,608) were excluded from the analysis. Females were excluded from the analysis because there were only four cancer cases among female participants. Pesticide exposure was assessed using responses about pesticide exposure captured on the enrollment questionnaires. Poisson regression was used to estimate individual RRs and 95% CIs, for the association between dicamba exposure and several cancers, adjusting for age, education, state of residence, smoking (pack years), family history of cancer, and total lifetime days of pesticide application. Lifetime exposure days were grouped into tertiles on the basis of the distribution among all cancer cases combined and the highest tertile was divided at the median to create the following categories for lifetime exposure days for all cancer types: No exposure, 1 to < 20 days, 20 to < 56 days, 56 to < 116 days, and ≥ 116 days. For the intensity-weighted lifetime exposure days analysis, categories of exposure included no exposure, 1 to < 86.6, 86.6 to < 344.3, 344.3 to < 739.2, and ≥ 739.2 intensity-weighted days. Among the 41,969

male pesticide applicators included in the analysis, 22,036 (52.5%) reported exposure to dicamba. Of the 85 NHL cases included in the analysis, 41 reported exposure to dicamba. No evidence of a significant positive association was reported for lifetime days of exposure and NHL at all exposure levels with the no exposed group and the low exposure group as the referent ($0.54 <$ all RRs < 1.75; all 95% CIs encompassed the null value of 1.0; with n = 7 – 18 exposed cases per exposure category; all p-trends > 0.05). Similarly, no evidence of a significant positive association was reported for all exposure categories of intensity-weighted lifetime exposure days and NHL with the no exposed group and the low exposure group as the referent ($0.46 <$ all RRs < 1.43; all 95% CIs encompassed the null value of 1.0; with n = 4 – 18 exposed cases per exposure category; all p-trends > 0.05). We note several categories had a very small number (< 10) of exposed cases per exposure category.

The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The ranking was based on the general strengths of the AHS, including its prospective design, ability to identify cancer cases through linkage to cancer registries, and exposure assessment approach which examined cumulative lifetime exposure to dicamba. Limitations were noted including the fact that the authors did not correct for/adjust for multiple comparison/multiple testing and that we would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported. We also note that the number of exposed cases per exposure category for several of the significant findings was small (n = 10).

- Leon et al. (2019) examined the association between pesticide exposure and cancer in agricultural workers, including dicamba and NHL, in a pooled analysis of data from three agricultural cohort studies, including AHS, as part of the AGRICOH. The AGRICOH is an international consortium of agricultural cohort studies that pool data to investigate health outcomes. The three cohorts included in this meta-analysis investigating effects of pesticide exposure on NHL were: (i) the AHS (data from private pesticide applicators only, commercial applicators excluded) of the United States; (ii) the Agriculture and Cancer (AGRICAN) cohort of France; and (iii) the Cancer in the Norwegian Agricultural Population (CNAP) cohort of residents of Norway. The three prospective cohorts assessed all incident cases of NHL and subtypes self-reported during follow-up (the date of enrollment for AHS and AGRICAN participants and 1993 for CNAP, the earliest year of follow-up) and through periodic data linkages to cancer and mortality registries. Specifically, for the AHS, this meta-analysis includes data from the AHS private pesticide applicators (commercial applicators were excluded), who enrolled between 1993 – 1997, with registry linkages until December 31, 2010 (North Carolina) and December 30, 2011 (Iowa). Dicamba exposure was assessed through self-report of ever exposure to pesticide active-ingredients (AHS) and self-report of crops cultivated combined with country-specific crop-exposure matrices (AGRICAN and CNAP); enrollment for the AGRICAN was 2005 – 2007 and for CNAP, owners and non-owners using a farm ("farm holders") and their families were included in at least one of five national agricultural and horticultural censuses performed during 1969, 1974, 1979, 1985, and 1989 by Statistics Norway. Cohort members were linked with appropriate cancer and mortality registries and the U.S National Death Index (AHS and CNAP only) to identify cases of NHL. Cox proportional hazard regression models were used to estimate the association between ever use of dicamba and incident NHL for each cohort, with never exposure as the referent. The AHS cohort specific regression model was adjusted for sex, state of residence, livestock (animal production), and pesticides terbufos, lindane, DDT, permethrin, dicamba, parathion, and carbaryl.[31] Resulting individual cohort estimates for dicamba were then combined using random effects meta-analysis. Among the 316,270 agricultural workers included in the combined study

[31] Each cohort Cox regression was adjusted for slightly different covariates: AGRICAN: sex, livestock, retirement status, number of selected types of crops for which pesticide treatment personally applied. CNAP: sex, livestock, dichlorvos, aldicarb, lindane, DDT, deltamethrin, mancozeb, linuron, glyphosate. AHS: sex, state, livestock, terbufos, lindane, DDT, permethrin, dicamba, parathion, carbaryl.

population, 2,430 were cases of NHL (493 cases were participants of the AHS cohort). The AHS cohort-specific risk estimate for the association between dicamba exposure and NHL was not reported. The authors reported no evidence of a significant positive association for dicamba ever exposure and overall NHL (i.e., all subtypes considered together) (HR = 1.04; 95% CI: 0.90, 1.19, with n = 815 exposed cases) and no evidence of a significant positive association for dicamba and any of the NHL subtypes in the meta-analysis ($0.81 < HR < 1.21$; all 95% CIs encompassed the null value of 1.0; with n = 73 – 815 exposed cases per category, p-trend > 0.05).

The quality of the study was ranked low based on the study quality criteria provided in the OPP Framework. Strengths of the study included the combination of three, very large international prospective cohort studies which increased the ability to detect epidemiological associations. Study limitations included differing exposure measurement methods used within the three studies, and potential exposure misclassification since the analysis of the combined cohort did not consider re-entry tasks through which contact with previously applied pesticides may have occurred. For example, only one of the two cohorts, the AHS cohort, uses actual exposure information collected by individuals through self-administered questionnaires; the French AGRICAN study and the Norwegian CNAP study instead rely on information from a crop-exposure matrix (CEM) to derive estimates of ever-exposure to glyphosate (among other pesticides). No actual pesticide exposure measurements were made in the AGRICAN or CNAP studies nor were specific questions about specific pesticide applications or application practices asked; instead, a variety of very general and very generic assumptions were made which likely lead to what might be a substantial degree of exposure misclassification. In addition, the study protocol was such that exposure misclassifications may have been exacerbated since analysis of the combined cohort did not consider re-entry tasks through which contact with previously applied pesticides may have occurred and which may equal or exceed pesticide exposure through application. An additional complication was that such re-entry work was not evenly distributed through the cohort. For example, 73% of the males and 56% of the females in AGRICAN reported performing re-entry work in vineyards which is a rarely reported crop in the US AHS (1%) -- and consisted itself of 97% male farmers. An additional limitation included the fact that the three cohorts differed in fundamental ways including the age of the participants (the AHS members tended to be younger at the start of follow-up) and there was a larger percentage of AGRICAN women participants. Further, different statistical adjustments were made depending on what covariates were measured in each of the individual cohorts: The AGRICAN study did not adjust for cigarette smoking, alcohol intake, or family history of cancer as the US AHS did but did adjust for animal production and for different pesticide active ingredients from those adjusted for and published in the US AHS study. Study authors did state that improvements were planned, specifically indicating that the specificity of the exposure assignments will be improved by incorporating the probability of pesticide use and adding parameters reflecting duration, frequency, and use intensity.

- Lerro et al. (2020) investigated the association between dicamba exposure and several cancers including NHL using data from the AHS prospective cohort that included additional cases and longer follow-up time than Samanic et al. (2006). The study population (n = 49,992) consisted of pesticide applicators living in Iowa and North Carolina who were enrolled in the AHS cohort and who reported information on dicamba exposure at enrollment and follow-up. Incident cancer cases were identified using Iowa and North Carolina state cancer registry files from enrollment (1993-1997) through December 2014 in North Carolina and December 2015 in Iowa. International Classification of Diseases for Oncology (ICD-0-2) codes were used to classify cancer sites. Dicamba exposure was assessed through the enrollment questionnaire (1993 – 1997) and the first follow-up interview five years after enrollment (1999 – 2005). Multiple imputation was used to estimate pesticide exposures at follow-up for individuals who did not complete the interview (n = 20, 968, 37%). Poisson regression was used to calculate relative risks and 95% confidence intervals for each category of intensity-

weighted days of dicamba use compared with no use, adjusting for age, race, sex, smoking, state, applicator type, education, imazethapyr use (Spearmen p = 0.49), and family history of cancer. Cumulative intensity-weighted days were categorized as no exposure or quartiles of exposure among all incident cancer cases for sites with > 20 exposed (no use, 5.0 – 449.5 days, 449.6 – 1260.0 days, 1260.1 – 3,698 days, >3,689 days) or based on the median, as no, low or high exposure for cancers and subtypes with 10–20 exposed cases (no use, 5.0 – 1,260.0 days, > 1,260.0 days). Among the 49,922 applicators, 26,412 (52.9%) reported dicamba exposure and among the 620 cases of NHL, 352 reported dicamba exposure. No evidence of a significant positive association was reported for NHL (all subtypes included) for any exposure category of cumulative intensity-weighted days of use (0.99 < RR < 1.25; all 95% CIs encompassed the null value of 1.0; with n = 78 – 96 exposed cases per category, p-trend > 0.05).

For the NHL subtype *mantel cell lymphoma*, evidence of a strong positive association was reported for both the low and the high exposure categories for cumulative intensity-weighted days of dicamba exposure and *mantel cell lymphoma*, among a small number of cases (*Low* – RR = 5.29; 95% CI: 3.41, 8.18; with n = 10 exposed cases; *High* – RR = 3.47; 95% CI: 2.06, 5.85; with n = 8 exposed cases; p-trend > 0.05), and no evidence of a significant exposure-response trend. For the NHL subtype *chronic/small lymphocytic leukemia*, evidence of a significant negative association was reported in the lowest exposure category among a small number of cases (*5.0 – 449.5 days* – RR = 0.74; 95% CI: 0.59, 0.92; with n = 17 exposed cases; p-trend < 0.05). No evidence of a significant positive association was reported for any exposure category of cumulative intensity-weighted days of dicamba exposure and *chronic/small lymphocytic leukemia* and other NHL subtypes (0.65 < RR < 2.07; all 95% CIs encompassed the null value of 1.0; with n = 4 – 20 exposed cases per category, p-trends > 0.05).

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The general strengths of the publication included the underlying prospective design of AHS, focus on U.S. agricultural populations, and availability of a U.S. registry to comprehensively identify cancer cases. Lerro et al. (2020) indirectly assessed dicamba exposure based on the AHS survey instrument. Limitations included over forty statistical tests between dicamba and different types of cancers without statistical correction for these multiple comparisons and that several of the statistically significant results would likely no longer be significant after statistical adjustment. Results from the ever/never use analysis were not reported. We also note that the number of cases per exposure category for several of the significant findings was very small (n ≤ 10). Finally, the mantle cell lymphoma finding is a first time (exploratory) finding and AHS practice is to require a second follow-on confirmatory finding to begin to consider making any conclusions. This latter point is acknowledged by the study authors who conclude that future epidemiologic work on dicamba should focus on replication of their study findings.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and NHL among men. Nine available epidemiologic studies (Cantor et al., 1992; McDuffie et al., 2001; McDuffie et al., 2005; De Roos et al., 2003; Hartge et al., 2005; Samanic et al., 2006; Czarnota et al., 2015; Lerro et al., 2020; Leon et al., 2019) examined the association between dicamba exposure and NHL.

Cantor et al. (1992) reported no evidence of a significant positive association between dicamba exposure and NHL among farmers in Iowa and Minnesota based on ever/never use. The study quality was ranked moderate and several limitations were noted including potential information bias due to use of proxy

respondents, recall bias, as the cases living with the outcome may have remembered certain past exposures more accurately than the controls, comparison of farmers to nonfarmers, different case and control selection methods and different pesticide exposure assessment methods (list of pesticides vs. voluntary recall). McDuffie et al. (2001, 2005) reported no evidence of a significant positive association between dicamba exposure and NHL among participants in the Cross-Canada Study of Pesticides and Health Study and both studies were ranked moderate. De Roos et al. (2003) reported no evidence of a significant positive association among farmers in the NCI pooled study population (from Iowa, Minnesota, Kansas, and Nebraska) when compared to non-farmers using the hierarchical regression statistical method, in addition to logistic regression. The overall quality of the study was ranked moderate. Hartge et. al. (2005) reported no evidence of a significant positive association between dicamba and NHL among a population-based case-control study. The study quality was ranked moderate. Limitations included potential recall bias due to cases potentially remembering exposure differently than controls, different selection methods used for cases and controls, and data imputation for missing data.

Czarnota et al. (2015) reported no evidence of a positive association between dicamba exposure and NHL in an analysis that combined data from four NCI SEER Study sites in a case-control analysis comparing the top three exposure quartiles to the lowest exposure quartile. Several limitations were noted including the exposure assessment approach which examined ever exposure to dicamba through dust samples collected from in the home a few years after cancer diagnosis was a limitation. Additionally, incomplete control for confounding by other chemical exposures in the individual analysis was considered a limitation. Finally, the number of cases and controls with dicamba exposure were not reported but would have been helpful in assessing the effect measures.

Samanic et al. (2006) reported no evidence of a significant positive association between dicamba and NHL (all subtypes combined) among pesticide applicators in the AHS prospective cohort. And, Lerro et al. (2020), similarly reported no evidence of a significant positive association for overall risk of NHL with longer follow-up time and a greater number of exposed cases. The quality of both studies was ranked moderate. Limitations for both Samanic et al. (2006) and Lerro et al. (2020) included that authors did not correct for/adjust for multiple comparison/multiple testing. We would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported. We also note that the number of exposed cases per exposure category for several of the significant findings was small (n ~ 10). For the NHL subtype, mantle cell lymphoma, Lerro et al. (2020) reported evidence of a strong positive association at both the low and high exposure levels, however this was among a very small (<10) number of exposed cases. The very small number of cases severely restricts the ability to interpret with confidence the observed effect estimates as well as our ability to assess the exposure-response relationship. AHS practice is to require a second follow-on confirmatory finding to begin to consider making any conclusions. Additionally, this was a first time (exploratory) finding and was acknowledged by the study authors who conclude that future epidemiologic work on dicamba should focus on replication of their study findings.

Lastly, Leon et al. (2019) examined the association between dicamba exposure among agricultural workers and non-Hodgkin lymphoma in a pooled analysis of data from three agricultural cohort studies, including the AHS cohort, as part of the AGRICOH consortium. The study reported no evidence of a significant positive association for dicamba exposure and NHL. The quality of the study was ranked low. Study limitations included differing exposure measurement methods used within the three studies, and potential exposure misclassification since the analysis of the combined cohort did not consider re-entry tasks through which contact with previously applied pesticides may have occurred. Additionally, the three cohorts differed in fundamental ways including the age of the participants (the AHS members tended to be younger at the start of follow-up) and by the different statistical adjustments made within the individual cohorts depending on what covariates were measured.

Multiple Myeloma

Five publications (Brown et al., 1993; Pahwa et al., 2006; Pahwa et al., 2012; Leon et al., 2019; Lerro et al., 2020) assessed the association between exposure to dicamba and multiple myeloma (MM).

- Brown et al. (1993) investigated the association between dicamba exposure and MM among men using data from three concurrent case-control studies conducted between 1981 – 1984 among MM cases in Iowa and non-Hodgkin lymphoma (NHL), and leukemia in Minnesota. MM cases included Caucasian men, ≥ 30 years old, who were diagnosed with MM between 1981 and 1984 and who lived in Iowa. Cases of MM were identified via the Iowa Health Registry and confirmed by a pathologist using pathology and laboratory reports. Controls were identified through random digit dialing, Medicare records, and state death certificates and included Caucasian men who did not have lymphatic or hematopoietic cancer. Controls were frequency-matched to the cases by age (within 5 years) and vital status (living or deceased) at time of interview. Exposure was assessed using a self-administered questionnaire; in-person interviews were conducted with next-of-kin if the study participant was deceased. Proxy respondents were used to complete in-person interviews for deceased cases (41%) and controls (30%). Logistic regression was used to calculate the OR and 95% CI for the association between dicamba ever use and MM, adjusting for age and vital status, with nonfarmers as the referent group. Education and smoking were considered but found not to be confounders. Of the total 173 MM cases and 650 controls, 10 cases and 43 controls reported exposure to dicamba. No evidence of a significant positive association was reported between dicamba ever use and MM, among a small number of cases, with the nonfarmers as the referent (OR = 1.30; 95% CI: 0.60, 2.80).

  The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths included the case-control study design, frequency matched cases to the controls, case ascertainment, and the in-person interviews. A main study limitation included the use of proxy respondents (41% of cases and 30% of controls) to collect pesticide exposure information. This limitation likely contributed to information bias and led to exposure misclassification. Another study limitation included potential recall bias, as the cases living with the outcome may have remembered certain past exposures more accurately than the controls. As a result, this recall bias likely led to exposure misclassification as well. Finally, authors compared the odds of cases of exposed farmers to nonfarmers, instead of exposed farmers to unexposed farmers, and any effects found from these comparisons might not be due to the chemical exposure but instead due to different risk of disease between two different subpopulations (farmers vs. nonfarmers).

- Pahwa et al. (2006) investigated the potential association between pesticides, including dicamba and MM, Hodgkin Lymphoma and Soft Tissue Sarcoma by conducting a population-based case-control study among men living in Canada known as the Cross-Canada Study of Pesticides and Health (CCSPH). The study population included males ≥ 19 years old who lived in one of six Canadian provinces and completed a postal questionnaire. Deceased participants were excluded from this analysis of the CCSPH data. Cases of multiple myeloma included those adult males diagnosed between September 1991 to December 1994 and were ascertained via provincial cancer registries or hospital ascertainment (Quebec only). Cases were validated by a pathologist who reviewed pathology slides. Controls were randomly selected males from either health insurance records, telephone directories (Ontario) or voters' lists (British Columbia), who resided in the same Canadian provinces as cases, and were matched to cases via age (± 2 years). A postal questionnaire was mailed to cases and controls to assess pesticide exposure, and follow-up telephone interviews regarding detailed pesticide use were conducted for each subject who reported more than 10 hours per year of pesticide

use. The response rate for cases and controls was 67.1% and 48.0%, respectively.[32] Exposure to dicamba included pesticides with dicamba as the main active ingredient (3,6 dichloro-2-methoxybenzoic acid) and mixtures of herbicides including dicamba as one of multiple active ingredients. Conditional logistic regression was used to calculate ORs and 95% CIs for dicamba and dicamba containing mixtures and MM, adjusting for age and province of residence. Among the those included in the analysis, 38 of the 342 MM cases reported exposure to any dicamba containing herbicide, and 131 of the 1,506 controls reported exposure to any dicamba containing herbicide. No evidence of a significant positive association was reported for any dicamba exposure (including mixtures)[33] and MM (OR = 1.32; 95% CI: 0.87, 2.00; with n = 38 exposed cases and n = 131 exposed controls). In an additional analysis that was limited to farm workers/dwellers only, no evidence of a positive association was reported between exposure to dicamba-containing herbicides and MM (OR = 1.00; 95% CI: 0.61, 1.65; with n = 27 exposed cases, n = 97 exposed controls). An additional sub-analysis that was conducted to determine if co-exposure to dicamba and DEET affected the risk of MM among participants reported no evidence of a significant positive association between those exposed do dicamba and DEET and MM (OR = 1.06; 95% CI: 0.63, 1.79; with n = 24 cases and n = 93 controls with exposure to dicamba and DEET).

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths included the study design, age matching the cases to the controls, and case ascertainment. Additionally, authors conducted a pilot study prior and a validation exercise for the study questionnaire as means to assess exposure accurately. Study limitations were related to the case-control study design and consisted of the potential for selection bias and recall bias. Another study limitation included potential recall bias, as the cases living with the outcome may have remembered certain past exposures more accurately than the controls. As a result, this recall bias may have led to exposure misclassification as well. Another limitation of the study was the response rate to the mailed questionnaires. Only 67.1% of the contacted cases and 48% of the contacted controls responded to the questionnaire and were included in the analysis. There may have been differences between those who responded and those who did not respond.

- Pahwa et al. (2012) investigated the potential association between exposure to pesticides, including dicamba, and MM in a population-based case-control study among men in six Canadian provinces.[34] Incident cases of MM included males >19 years old with a first-time diagnosis of multiple myeloma (ICD-0 M9732/3) between September 1, 1991 and December 31, 1994. Case were identified using provincial cancer registries, with the exception of Quebec where cases were ascertained based on hospital records. Study pathologists confirmed 36.5% of these cases using available pathology materials. Controls included males ≥ 19 years old who were randomly selected from either health insurance records (Alberta, Saskatchewan, Manitoba, and Quebec), telephone listings (Ontario), or voter's lists (British Columbia) and were matched to cases based on age and residence. Pesticide exposure was assessed using a self-administered questionnaire that also included questions about demographic information, medical history, smoking history, and lifetime occupational and non-occupational (hobbies etc.) history and pesticide exposure. An additional telephone interview was administered to all participants with ≥10 hours of reported lifetime pesticide use and a 15% random

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[32] McDuffie, H. H., Pahwa, P., Robson, D., Dosman, J. A., Fincham, S., Spinelli, J. J., & McLaughlin, J. R. (2005). Insect repellents, phenoxyherbicide exposure, and non-Hodgkin's lymphoma. J Occup Environ Med, 47(8), 806-816. doi:10.1097/01.jom.0000167260.80687.78

[33] For any dicamba exposure, authors included exposures to dicamba as the sole active ingredient and to products that were mixtures that contained active ingredients in addition to dicamba such as: dicamba and glyphosate; and dicamba, 2,4-D, and mecoprop.

[34] The six Canadian provinces were Quebec, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia.

sample of the remaining population who completed the self-questionnaire. Overall, participation rates were 58% for contacted cases and 48% for contacted controls, yielding 342 cases and 1,506 controls. Conditional logistic regression was used to determine ORs and 95% CIs for individual pesticides including dicamba, adjusted for age, province of residence, and medical history variables (history of the following: measles, mumps, allergies, arthritis, shingles, and a positive family history of cancer in a first-degree relative). No evidence of a significant positive associaton was observed between exposure to dicamba as a chemical class and MM (OR = 1.33; 95% CI: 0.98, 1.80; with n = 38 exposed cases and n = 131 exposed controls). Similar results were reported when exposure to individual dicamba herbicides (such as Banvel or Target) was considered in the analysis (OR = 1.24; 95% CI: 0.64, 2.42; with n = 14 exposed cases).

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths included the study design, age matching the cases to the controls, and case ascertainment. Additionally, authors conducted a pilot study prior and a validation exercise for the study questionnaire as means to assess exposure accurately. Study limitations were related to the case-control study design and consisted of the potential for selection bias and recall bias as the cases living with the outcome may have remembered certain past exposures more accurately than the controls. As a result, this recall bias may have led to exposure misclassification as well. Another limitation of the study was the response rate to the mailed questionnaires. Only 67.1% of the contacted cases and 48% of the contacted controls responded to the questionnaire and were included in the analysis. There may have been differences between those who responded and those who did not respond.

- Leon et al. (2019) examined the association between pesticide exposure and cancer in agricultural workers, including dicamba and MM, in a pooled analysis of data from three agricultural cohort studies, including AHS, as part of the AGRICOH as described in more detail above. Briefly, this study includes a pooled analysis of data from three cohorts to examine the association between exposure to pesticides, including dicamba, and MM. The three prospective cohorts assessed all incident cases of NHL and subtypes self-reported during follow-up (the date of enrollment for AHS and AGRICAN participants and 1993 for CNAP, the earliest year of follow-up) and through periodic data linkages to cancer and mortality registries. Specifically, for the AHS, this meta-analysis includes data from the AHS private pesticide applicators (commercial applicators were excluded), who enrolled between 1993 – 1997, with registry linkages until December 31, 2010 (North Carolina) and December 30, 2011 (Iowa). Dicamba exposure was assessed through self-report of ever exposure to pesticide active-ingredients (AHS) and self-report of crops cultivated combined with country-specific crop-exposure matrices (AGRICAN and CNAP); enrollment for the AGRICAN was 2005 – 2007 and for CNAP, owners and non-owners using a farm ("farm holders") and their families were included in at least one of five national agricultural and horticultural censuses performed during 1969, 1974, 1979, 1985, and 1989 by Statistics Norway. Cohort members were linked with appropriate cancer and mortality registries and the U.S National Death Index (AHS and CNAP only) to identify cases of NHL. Cox proportional hazard regression models were used to estimate the association between ever use of dicamba and incident NHL for each cohort, with never exposure as the referent. The AHS cohort specific regression model was adjusted for sex, state of residence, livestock (animal production), and pesticides terbufos, lindane, DDT, permethrin, dicamba, parathion, and carbaryl.[35] Resulting individual cohort estimates for dicamba were then combined using random effects meta-

[35] Each cohort Cox regression was adjusted for slightly different covariates: AGRICAN: sex, livestock, retirement status, number of selected types of crops for which pesticide treatment personally applied. CNAP: sex, livestock, dichlorvos, aldicarb, lindane, DDT, deltamethrin, mancozeb, linuron, glyphosate. AHS: sex, state, livestock, terbufos, lindane, DDT, permethrin, dicamba, parathion, carbaryl.

analysis. Among the 316,270 agricultural workers included in the combined study population, 2,430 were cases of NHL (493 cases were participants of the AHS cohort). Authors considered MM a subtype of NHL. No evidence of a significant positive association was reported for dicamba ever exposure and MM among all participants in the analysis (HR = 1.21; 95% CI: 0.93, 1.59, with n = 179 exposed cases). And similarly, no evidence of a significant positive association was reported for the association between dicamba exposure and MM among the AHS cohort (HR = 1.28; 95% CI: 0.77, 2.13; with n = 47 exposure cases in the AHS cohort).

The quality of the study was ranked low based on the study quality criteria provided in the OPP Framework. Strengths of the study included the combination of three, very large international prospective cohort studies which increased the ability to detect epidemiological associations. Study limitations included differing exposure measurement methods used within the three studies, and potential exposure misclassification since the analysis of the combined cohort did not consider re-entry tasks through which contact with previously applied pesticides may have occurred. For example, only one of the two cohorts, the AHS cohort, uses actual exposure information collected by individuals through self-administered questionnaires; the French AGRICAN study and the Norwegian CNAP study instead rely on information from a crop-exposure matrix (CEM) to derive estimates of ever-exposure to glyphosate (among other pesticides). No actual pesticide exposure measurements were made in the AGRICAN or CNAP studies nor were specific questions about specific pesticide applications or application practices asked; instead, a variety of very general and very generic assumptions were made which likely lead to what might be a substantial degree of exposure misclassification. In addition, the study protocol was such that exposure misclassifications may have been exacerbated since analysis of the combined cohort did not consider re-entry tasks through which contact with previously applied pesticides may have occurred and which may equal or exceed pesticide exposure through application. An additional complication was that such re-entry work was not evenly distributed through the cohort. For example, 73% of the males and 56% of the females in AGRICAN reported performing re-entry work in vineyards which is a rarely reported crop in the US AHS (1%) -- and consisted itself of 97% male farmers. An additional limitation included the fact that the three cohorts differed in fundamental ways including the age of the participants (the AHS members tended to be younger at the start of follow-up) and there was a larger percentage of AGRICAN women participants. Further, different statistical adjustments were made depending on what covariates were measured in each of the individual cohorts: The AGRICAN study did not adjust for cigarette smoking, alcohol intake, or family history of cancer as the US AHS did but did adjust for animal production and for different pesticide active ingredients from those adjusted for and published in the US AHS study.

- Lerro et al. (2020) investigated the association between dicamba exposure and several cancers including MM using data from the AHS prospective cohort. The study population (n = 49,992) consisted of pesticide applicators living in Iowa and North Carolina who were enrolled in the AHS cohort and who reported information on dicamba exposure at enrollment and follow-up. Incident cancer cases were identified using Iowa and North Carolina state cancer registry files from enrollment (1993-1997) through December 2014 in North Carolina and December 2015 in Iowa. International Classification of Diseases for Oncology (ICD-0-2) codes were used to classify cancer sites. Dicamba exposure was assessed through the enrollment questionnaire (1993 – 1997) and the first follow-up interview five years after enrollment (1999 – 2005). Multiple imputation was used to estimate pesticide exposures at follow-up for individuals who did not complete the interview (n = 20, 968, 37%). Poisson regression was used to calculate relative risks and 95% confidence intervals for each category of intensity-weighted days of dicamba use compared with no use, adjusting for age, race, sex, smoking, state, applicator type, education, imazethapyr use (Spearmen p = 0.49), and family history of cancer. Cumulative intensity-weighted days were categorized as no exposure or quartiles of

intensity-weighted days of exposure among all incident cancer cases for sites with > 20 exposed (no use, 5.0 – 449.5 days, 449.6 – 1260.0 days, 1260.1 – 3,698 days, >3,689 days) or based on the median, as no, low or high exposure for cancers and subtypes with 10–20 exposed cases (no use, 5.0 – 1,260.0 days, > 1,260.0 days). Among the 49,922 applicators, 26,412 (52.9%) reported dicamba exposure and among the 136 cases of MM combined, 72 reported dicamba exposure. No evidence of a significant positive association was reported for any exposure category for cumulative intensity-weighted days of dicamba exposure and MM (1.24 < all RRs < 1.42; all 95% CIs encompassed the null value of 1.0; with n = 15 – 20 cases per exposure category).

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The publication benefitted from the general strengths of the AHS including the prospective design, case ascertainment using cancer registries, and the exposure assessment. Multiple comparisons were performed without correction or adjustment for multiple comparison/multiple testing and this was considered a limitation. We would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and multiple myeloma (MM). Five publications (Brown et al., 1993; Pahwa et al., 2006; Pahwa et al., 2012; Leon et al., 2019; Lerro et al., 2020) assessed the association between exposure to dicamba and MM. Brown et al. (1993), reported no evidence of a significant positive association between dicamba and MM in a case-control study in Iowa. The study quality was ranked moderate. Study limitations included the use of proxy respondents and recall bias which likely led to exposure misclassification and compared two different subpopulations (farmers vs. nonfarmers) who have a different risk of disease. Pahwa et al. (2006) and Pahwa et al. (2012) each reported no evidence of a significant positive association between dicamba exposure and MM in the Cross-Canada Study of Pesticides and Health case-control study. The study quality of both studies was moderate and study limitations included potential for selection bias, recall bias. Leon et al. (2019) examined the association between dicamba exposure and MM among the three pooled agricultural cohort studies that make up the AGRICOH. One of the study populations included those of the AHS. No evidence of a significant positive association was reported. And the study was ranked low due to limitations with the pesticide exposure assessment and potential misclassification, methods used to measure covariates and lack of adjustment for important potential confounders. Finally, Lerro et al. (2020) reported no evidence of a significant positive association between intensity-weighted days of dicamba exposure and MM among participants in the large AHS prospective cohort. This study was ranked moderate quality. While the study benefited from the prospective design, case ascertainment, and exposure assessment of the AHS, limitations were noted including multiple comparisons without adjustment.

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Melanoma

Two studies (Samanic et al., 2006; Lerro et al., 2020) assessed the association between exposure to dicamba and melanoma.

- Samanic et al. (2006) examined the association between dicamba exposure and several cancers, including melanoma among pesticide applicators in the AHS prospective cohort. The study population included male pesticide applicators living in Iowa and North Carolina who completed the

AHS enrollment questionnaires and had complete data on dicamba and covariates. Cases of incident cancer (first primary cancer) diagnosed between enrollment (1993 - 1997) and December 31, 2002 were identified via linkage to state cancer registries. Those who reported cancer at the time of enrollment (n = 1,075) or were missing information about dicamba (n = 6,362); or missing information about covariates (n = 6,608) were excluded from the analysis. Females were excluded from the analysis because there were only four cancer cases among female participants. Pesticide exposure was assessed using responses about pesticide exposure captured on the enrollment questionnaires. Poisson regression was used to estimate individual RRs and 95% CIs, for the association between dicamba exposure and several cancers, adjusting for age, education, state of residence, smoking (pack years), family history of cancer, and total lifetime days of pesticide application. Lifetime exposure days were grouped into tertiles on the basis of the distribution among all cancer cases combined and the highest tertile was divided at the median to create the following categories for lifetime exposure days for all cancer types: No exposure, 1 to < 20 days, 20 to < 56 days, 56 to < 116 days, and ≥ 116 days. For the intensity-weighted lifetime exposure days analysis, categories of exposure included no exposure, 1 to < 86.6, 86.6 to < 344.3, 344.3 to < 739.2, and ≥ 739.2 intensity-weighted days. Among the 41,969 male pesticide applicators included in the analysis, 22,036 (52.5%) reported exposure to dicamba. Of the 72 melanoma cases included in the analysis, 40 reported exposure to dicamba. No evidence of a significant positive association was reported for any exposure level of lifetime days of dicamba use with the no exposed group or the low exposed group as the referent (0.72 < all RRs < 1.65; all 95% CIs encompassed the null value of 1.0; with n = 6 - 18 cases per exposure category; all p-trends > 0.05). For intensity-weighted lifetime days of dicamba use, no evidence of a significant positive association was reported for all exposure categories of intensity-weighted lifetime exposure days with the no exposed group and the low exposure group as the referent (0.77 < all RRs < 1.80; all 95% CIs encompassed the null value of 1.0; with n = 5 - 18 cases per exposure category; all p-trends > 0.05).

The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The ranking was based on the general strengths of the AHS, including its prospective design, ability to identify cancer cases through linkage to cancer registries, and exposure assessment approach which examined cumulative lifetime exposure to dicamba. Limitations were noted including the fact that the authors did not correct for/adjust for multiple comparison/multiple testing and that we would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported. We also note that the number of exposed cases was very small which severely restricts the ability to interpret with confidence the observed RRs as well as the ability to assess the exposure-response relationship.

- In a follow-up study with longer follow-up time and additional cases, Lerro et al. (2020) investigated the association between dicamba exposure and several cancers including melanoma among the AHS prospective cohort. The study population (n = 49,992) consisted of pesticide applicators living in Iowa and North Carolina who were enrolled in the AHS cohort and who reported information on dicamba exposure at enrollment and follow-up. Incident cancer cases were identified using Iowa and North Carolina state cancer registry files from enrollment (1993-1997) through December 2014 in North Carolina and December 2015 in Iowa. International Classification of Diseases for Oncology (ICD-0-2) codes were used to classify cancer sites. Dicamba exposure was assessed through the enrollment questionnaire (1993 – 1997) and the first follow-up interview five years after enrollment (1999 – 2005). Multiple imputation was used to estimate pesticide exposures at follow-up for individuals who did not complete the interview (n = 20, 968, 37%). Poisson regression was used to calculate relative risks and 95% confidence intervals for each category of intensity-weighted days of dicamba use compared with no use, adjusting for age, race, sex, smoking, state, applicator type, education, imazethapyr use (Spearmen p = 0.49), and family history of cancer. Cumulative intensity-

weighted days were categorized as no exposure or quartiles of intensity-weighted days of exposure among all incident cancer cases for sites with > 20 exposed (no use, 5.0 – 449.5 days, 449.6 – 1260.0 days, 1260.1 – 3,698 days, >3,689 days) or based on the median, as no, low or high exposure for cancers and subtypes with 10–20 exposed cases (no use, 5.0 – 1,260.0 days, > 1,260.0 days). Among the 49,922 applicators, 26,412 (52.9%) reported dicamba exposure and among the 364 cases of melanoma, 197 reported dicamba exposure. No evidence of a significant positive association was reported for any exposure category (0.94 < RR < 1.07; all 95% CIs encompassed the null value of 1.0; with n = 48 - 51 exposed cases per exposure category; p-trend = 0.91), with the no exposure group as the referent, and no evidence of a significant exposure-response trend.

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The general strengths of the publication included the underlying prospective design of the AHS, focus on U.S. agricultural populations, and availability of a U.S. cancer registry to comprehensively identify cancer cases. Authors performed multiple comparisons however did not correct for multiple comparison. We would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and melanoma. This determination was based off of two available studies (Samanic et al., 2006; Lerro et al., 2020) that investigated the association between dicamba exposure and melanoma in the AHS prospective cohort. Samanic et al. (2006) reported no evidence of a significant positive association based on lifetime days and intensity-weighted lifetime days of dicamba exposure with no evidence of statistically significant p-trends. The study quality was ranked moderate and several strengths were noted including the prospective cohort study design as part of the AHS, the ascertainment of cancer cases using established cancer registries, and the strengths of the AHS exposure assessment approach. The multiple comparisons performed without statistical correction for multiple comparisons was considered a limitation. Lerro et al. (2020) reported no evidence of a significant positive exposure between intensity weighted lifetime days of dicamba and melanoma among the AHS prospective cohort with more cases and longer follow-up time than Samanic et al. (2006). Lerro et al. (2020) also benefited from the strengths of the AHS including the exposure and outcome assessment, however, the authors performed multiple comparisons without statistical correction for multiple comparisons. This was considered a limitation.

Pancreatic Cancer

The association between dicamba and pancreatic cancer was evaluated in two AHS studies (Andreotti et al., 2009; Lerro et al., 2020).

- Andreotti et al. (2009) conducted a case-control analysis of the AHS cohort to evaluate the association between pesticides, including dicamba, and pancreatic cancer incidence. The study population consisted of licensed private and commercial pesticide applicators and their spouses enrolled in the AHS. Incident pancreatic cancer cases diagnosed from enrollment (1993-1997) through 2004 were identified through state cancer registry files in Iowa and North Carolina. Participants with any cancer reported at enrollment were excluded from the analysis. Pesticide exposure (ever/never) was assessed via a self-administered questionnaire completed at enrollment and shortly thereafter. Unconditional logistic regression was used to calculate ORs and 95% CIs for the association between ever/never exposure to dicamba among spouses and pesticide applicators,

adjusting for age, smoking, diabetes, and applicator type. Further analyses stratified IWLD of dicamba use among applicators (for spouses, only ever/never pesticide use was available), and two categories (low- and high-use) were created based on median level among controls. ORs and 95% CIs were reported for each category with the non-exposed group (never use) as the referent, adjusting for diabetes, age, and smoking status (never, past, current). Among the study population (n = 82,596), there were 93 incident pancreatic cancer cases (64 applicators, 29 spouses), and of those cases with information on dicamba use, 23 reported ever exposure to dicamba and 57 reported no dicamba exposure. Of the 82,503 pancreatic cancer-free controls, 25,000 reported ever exposure to dicamba and 50,606 reported no dicamba exposure. No evidence of a positive association was reported between dicamba exposure and pancreatic cancer among pesticide applicators and spouses (OR = 0.90; 95% CI: 0.60, 1.60, with n = 23 exposed cases) based on ever/never use. For the cumulative intensity-weighted days analysis, no evidence of a significant positive association was reported for the association between dicamba and pancreatic cancer among pesticide applicators in either the low or the high exposure group with the never exposure group as the referent and there was no evidence of an exposure-response trend (*Low* – OR = 1.40; 95% CI: 0.80, 2.70, with n = 16 exposed cases; *High* – OR = 0.50; 95% CI: 0.20, 1.30, with n = 5 exposed cases, p-trend = 0.32).

The overall quality of the study was ranked high based on the study quality criteria provided in the OPP Framework. The ranking was based on the general strengths of the AHS, including its prospective design, ability to identify cancer cases through linkage to cancer registries, and exposure assessment approach which examined cumulative lifetime exposure to dicamba.

- In a separate study with longer follow-up time, Lerro et al. (2020) investigated the association between dicamba exposure and several cancers including pancreatic cancers using data from the AHS prospective cohort. The study population (n = 49,992) consisted of pesticide applicators living in Iowa and North Carolina who were enrolled in the AHS cohort and who reported information on dicamba exposure at enrollment and follow-up. Incident cancer cases were identified using Iowa and North Carolina state cancer registry files from enrollment (1993-1997) through December 2014 in North Carolina and December 2015 in Iowa. International Classification of Diseases for Oncology (ICD-0-2) codes were used to classify cancer sites. Dicamba exposure was assessed through the enrollment questionnaire (1993 – 1997) and the first follow-up interview five years after enrollment (1999 – 2005). Multiple imputation was used to estimate pesticide exposures at follow-up for individuals who did not complete the interview (n = 20, 968, 37%). Poisson regression was used to calculate relative risks and 95% confidence intervals for each category of intensity-weighted days of dicamba use compared with no use, adjusting for age, race, sex, smoking, state, applicator type, education, imazethapyr use (Spearmen p = 0.49), and family history of cancer. The analysis for pancreatic cancer was also adjusted for pack-years smoked (tertiles by smoking status) and BMI. Cumulative intensity-weighted days were categorized as no exposure or quartiles of intensity-weighted days of exposure among all incident cancer cases for sites with > 20 exposed (no use, 5.0 – 449.5 days, 449.6 – 1260.0 days, 1260.1 – 3,698 days, >3,689 days) or based on the median, as no, low or high exposure for cancers and subtypes with 10–20 exposed cases (no use, 5.0 – 1,260.0 days, > 1,260.0 days). Among the 49,922 applicators, 26,412 (52.9%) reported dicamba exposure and among the 163 cases of pancreatic cancer, 77 reported dicamba exposure. No evidence of a significant positive association was reported for any exposure category of intensity-weighted days of dicamba exposure and pancreatic cancer (0.88 < RR < 1.33; all 95% CIs encompassed the null value of 1.0; with n = 16 – 25 exposed cases per exposure category; p-trend = 0.92), with the no exposure group as the referent, and no evidence of a significant exposure-response trend.

  The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The general strengths of the publication included the underlying prospective

design of the AHS, focus on U.S. agricultural populations, and availability of a U.S. cancer registry to comprehensively identify cancer cases. Authors performed multiple comparisons however did not correct for multiple comparison. We would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and pancreatic cancer. Two studies (Andreotti et al., 2009; Lerro et al., 2020) were identified that assessed the association between dicamba exposure and pancreatic cancer among the AHS prospective cohort. Andreotti et al. (2009) reported no evidence of a positive association based on ever use and no evidence of a significant positive association between dicamba intensity weighted lifetime days of use and pancreatic cancer. We not that both findings were among a very small number of exposed cases which severely restricts the ability to interpret with confidence the observed odds ratios. In a separate study with longer follow-up time, Lerro et al. (2020) reported no evidence of a significant positive association between intensity weighted lifetime days of dicamba and pancreatic cancer. Both studies benefited from the general strengths of the AHS including the exposure assessment, and outcome ascertainment via state cancer registries. Lerro was ranked moderate quality and it was noted that multiple comparisons were performed without correction.

Prostate Cancer

Nine studies (Alavanja et al., 2003; Samanic et al., 2006; Band et al., 2011; Barry et al., 2011; Barry et al., 2012; Koutros et al., 2011; Christensen et al., 2016; Koutros et al., 2013; Lerro et al., 2020) examined the relationship between dicamba exposure and prostate cancer.

- Alavanja et al. (2003) evaluated the potential association between pesticide exposure, including dicamba and incident prostate cancer in a prospective cohort study. The study population (n = 55,332) included male pesticide applicators in the AHS living in Iowa and North Carolina. Incident prostate cancer cases were identified at study enrollment (1993-1997) through December 31, 1999, using cancer registry files in Iowa and North Carolina, and vital status was ascertained using state death records and the National Death Index. Pesticide exposure was assessed through self-administered questionnaires, one completed at study enrollment and a second more detailed questionnaire completed at home shortly afterwards. Among the 55,332 participants included in this analysis, 566 incident prostate cancer cases were reported, and 213 of the cases reported dicamba exposure. Unconditional logistic regression was used to estimate ORs and 95% CIs for the association between dicamba exposure and incident prostate cancer, adjusting for family history of prostate cancer and age. No evidence of a significant exposure-response relationship was reported for the association between cumulative exposure to dicamba and prostate cancer (data not reported). The results of the analysis between ever/never use of dicamba and prostate cancer were not reported. Potential effect modification of a family history of prostate cancer on the association between permethrin and prostate cancer was assessed via logistic model with a cross product term (family history × pesticide exposure) and found there was not a significant interaction between family history of prostate cancer and exposure (interaction OR = 1.51, 95% CI: 0.95, 2.43; p-value > 0.05; with n = 163 exposed cases with no family history of prostate cancer and n = 50 exposed cases with family history of prostate cancer). No evidence of a significant positive association was reported for dicamba exposure and incident prostate cancer among those with a family history of prostate cancer (OR = 1.35; 95% CI: 0.88, 2.08; with n = 50 exposed cases). And no evidence of a positive association was reported for those without a family history of prostate cancer (OR = 0.95; 95% CI: 0.77, 1.17; with n = 163 exposed cases).

The overall quality of the study was ranked high based on the study quality criteria provided in the OPP Framework. The ranking was based on the general strengths of the AHS, including its prospective design, ability to identify cancer cases through linkage to cancer registries, and exposure assessment approach which examined cumulative lifetime exposure to dicamba. More detailed reporting of the results for all pesticides assessed may have been helpful.

- Samanic et al. (2006) examined the association between dicamba exposure and several cancers, including prostate cancer among pesticide applicators in the AHS prospective cohort. The study population included male pesticide applicators living in Iowa and North Carolina who completed the AHS enrollment questionnaires and had complete data on dicamba and covariates. Cases of incident cancer (first primary cancer) diagnosed between enrollment (1993 - 1997) and December 31, 2002 were identified via linkage to state cancer registries. Those who reported cancer at the time of enrollment (n = 1,075) or were missing information about dicamba (n = 6,362); or missing information about covariates (n = 6,608) were excluded from the analysis. Females were excluded from the analysis because there were only four cancer cases among female participants. Pesticide exposure was assessed using responses about pesticide exposure captured on the enrollment questionnaires. Poisson regression was used to estimate individual RRs and 95% CIs, for the association between dicamba exposure and several cancers, adjusting for age, education, state of residence, smoking (pack years), family history of cancer, and total lifetime days of pesticide application. Lifetime exposure days were grouped into tertiles on the basis of the distribution among all cancer cases combined and the highest tertile was divided at the median to create the following categories for lifetime exposure days for all cancer types: No exposure, 1 to < 20 days, 20 to < 56 days, 56 to < 116 days, and ≥ 116 days. For the intensity-weighted lifetime exposure days analysis, categories of exposure included no exposure, 1 to < 86.6, 86.6 to < 344.3, 344.3 to < 739.2, and ≥ 739.2 intensity-weighted days. Among the 41,969 male pesticide applicators included in the analysis, 22,036 (52.5%) reported exposure to dicamba. Of the 694 prostate cancer cases included in the analysis, 351 reported exposure to dicamba. No evidence of a significant positive association was reported for lifetime days of exposure at all exposure levels with the no exposed group and the low exposure group as the referent (0.94 < all RRs < 1.10; all 95% CIs encompassed the null value of 1.0; with n = 67 - 106 exposed cases per exposure category; all p-trends > 0.05). Similarly, no evidence of a significant positive association was reported for all exposure categories of intensity-weighted lifetime exposure days with either the no exposed group and the low exposure group as the referent (0.95 < all RRs < 1.17; all 95% CIs encompassed the null value of 1.0; with n = 59 – 115 exposed cases per exposure category; all p-trends > 0.05).

  The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The ranking was based on the general strengths of the AHS, including its prospective design, ability to identify cancer cases through linkage to cancer registries, and exposure assessment approach which examined cumulative lifetime exposure to dicamba. Limitations were noted including the fact that the authors did not correct for multiple comparison/multiple testing and that we would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported.

- Barry et al. (2011) and Barry et al. (2012) investigated the association between pesticide exposures including dicamba and prostate cancer, and genetic variation among Base Excision Repair (BER) and the nucleotide excision repair (NER) pathway genes using a nested case-control study within the AHS. The study population included white male pesticide applicators, living in Iowa or North Carolina, who were diagnosed with prostate cancer between enrollment (1993 – 1997) and 2004. Cases were ascertained through state cancer registries. Controls included white male applicators with no previous cancer history (except non-melanoma skin cancer), who were frequency-

matched to cases (2:1) by birth date (±1 year). Pesticide exposure, including dicamba, was assessed through two self-administered questionnaires at study enrollment and shortly thereafter (1993 - 1997), and exposure was classified into intensity-weighted lifetime days of use and categorized into non-exposed, low, and high exposure groups. Unconditional logistic regression was used to investigate the association between dicamba and prostate cancer risk, adjusting for state and age and estimated associations between BER gene variant alleles and prostate cancer. We only report on findings between dicamba exposure and risk of prostate cancer here as that is the main focus of this document. Among the total cases (n = 776) and controls (n = 1,444), 348 cases and 723 controls reported dicamba exposure and 324 cases and 573 controls reported no dicamba exposure, respectively. No evidence of a positive association was reported between dicamba exposure and prostate cancer among white male pesticide applicators in either the low or high exposure categories, with the non-exposed group as the referent (*Low* – OR = 0.81; 95% CI: 0.63, 1.04; with n = 172 exposed cases and n = 362 exposed controls; *High* – OR = 0.82; 95% CI: 0.64, 1.06; with n = 176 cases and n = 361 controls; p-trend = 0.69).

The overall quality of the study was ranked high based on the study quality criteria provided in the OPP Framework. The ranking was based on the general strengths of the AHS, including its prospective design, ability to identify cancer cases through linkage to cancer registries, and exposure assessment approach which examined cumulative lifetime exposure to dicamba.

- Koutros et al. (2011) evaluated the association between specific pesticides including dicamba and prostate cancer among male licensed pesticide applicators in a nested case-control analysis within the AHS prospective cohort. The study population (n = 2,500) included male pesticide applicators living in Iowa and North Carolina, enrolled in the AHS prospective cohort. Incident cases were determined beginning at study enrollment (1993-1997) through 2004 using cancer registry files from Iowa and North Carolina, and vital status was confirmed through the state death registries and the National Death Index. At follow-up, men were also asked to submit a DNA sample from buccal cells. Controls (n = 1,444) included pesticide applicators (males only) who had not been previously diagnosed with prostate cancer, were not deceased at the time of follow-up, and had provided a DNA sample of buccal cells. The controls were frequency-matched to the cases (2:1) via birthdate (+/- 1 year). Exposure was assessed using data from two self-administered questionnaires completed at enrollment to determine dicamba usage, and to further classify dicamba usage by lifetime exposure days. Lifetime exposure days were categorized as non-exposed, low, or high exposure, based on the median cut-point determined from the distribution of lifetime exposure days of both the controls and cases. Unconditional logistic regression was used to calculate ORs and 95% CIs for the association between dicamba exposures and prostate cancer, adjusted for state, age, and family history of prostate cancer. Among the 776 cases and 1,444 controls, 352 cases and 375 controls reported dicamba exposure. No evidence of a positive association was reported between dicamba exposure and prostate cancer in either the low or high exposure categories (*Low* - OR = 0.78; 95% CI: 0.61, 1.00; with n = 171 exposed cases and n = 368 exposed controls; *High* - OR = 0.82; 95% CI: 0.63, 1.05; with n = 181 exposed cases and n = 360 exposed controls; p-trend = 0.318).

  The overall quality of the study was ranked high based on the study quality criteria provided in the OPP Framework. The ranking was based on the general strengths of the AHS, including its prospective design, ability to identify cancer cases through linkage to cancer registries, and exposure assessment approach which examined cumulative lifetime exposure to dicamba.

- Koutros et al. (2013) investigated the potential association between specific pesticides including dicamba, and prostate cancer adding cases through 2007.[36] The study population (n = 54,412) included male pesticide applicators participating in the AHS. Pesticide exposure was assessed by information obtained via self-administered questionnaires, and this information was used to calculate lifetime pesticide usage for 50 pesticides. Exposure values were modified by an intensity factor to account for the variation in pesticide application practices to produce an estimate of intensity-weighted lifetime days of exposure metric. Incident prostate cancer cases were identified through cancer registry files in Iowa and North Carolina, and cases diagnosed between study enrollment (1993-1997) until December 31, 2007 were included in this analysis. Incident cancer cases were then subdivided into prostate cancer or aggressive prostate cancer based on the Gleason score tumor ranking scale provided by a medical pathologist.[37,38] Among the total study participants (n = 54,412), 838 cases and 25,516 non-cases reported dicamba exposure. A Poisson regression was used to calculate RRs, adjusting for state, age, race, and family history of prostate cancer, smoking, fruit servings, and leisure-time physical activity in the winter. Four quartiles were constructed for prostate cancer and aggressive prostate cancer based on exposure (n = 208 - 212 cases per quartile for prostate cancer and n = 99 - 380 cases per quartile for aggressive prostate cancer), and RRs were reported for each quartile. No evidence of a significant positive association was observed for dicamba exposure and prostate cancer or aggressive prostate cancer for any of the exposure categories ($0.82 \leq RRs \leq 1.04$; all CIs encompassed the null value of 1.00), and there was no evidence of a linear (monotonic) trend across categories for total prostate cancer and aggressive prostate cancer (p-trends > 0.05). In the analysis that considered cumulative lifetime days of dicamba exposure and prostate cancer by family history of prostate cancer, no evidence of a significant positive association was reported for any exposure category for either cumulative lifetime days or intensity-weighted lifetime days of exposure ($0.88 \leq RRs \leq 1.20$; all CIs encompassed the null value of 1.00), and there was no evidence of a linear (monotonic) trend across categories for total prostate cancer and aggressive prostate cancer (p-trends > 0.05) and no evidence of an interaction (p-interaction = 0.22).

  The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The ranking was based on the general strengths of the AHS, including its prospective design, ability to identify cancer cases through linkage to cancer registries, and exposure assessment approach which examined cumulative lifetime exposure to dicamba. Study limitations included missing the Gleason score among the cases in North Carolina (~30% of the cases) which could have led to underestimation of severity of prostate cancer, the Gleason scores used in the study were not standardized by the centralized pathologic review, and the potential for exposure misclassification.

- In a separate study, Christensen et al. (2016) evaluated the potential association between pesticide exposures, including dicamba, and prostate cancer and modifications of risk by single-nucleotide polymorphisms on sex hormones using a nested case-control study within the AHS prospective cohort. The study population included white male pesticide applicators living in Iowa or North Carolina. Cases included white male AHS study participants who were cancer-free at enrollment, had physician-diagnosed prostate cancer between enrollment (1993 – 1997) and 2004, and provided a buccal cell sample later used for DNA testing. Cases were ascertained through state cancer registries.

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[36] Koutros et al. (2013) is a follow-up to the following study: Alavanja, M. C., Samanic, C., Dosemeci, M., Lubin, J., Tarone, R., Lynch, C. F., Knott, C., Thomas, K., Hoppin, J.A., Barker, J., Sandler, D.P., Blair, A., & Coble, J. (2003). Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. *American journal of epidemiology*, *157*(9), 800-814.

[37] Johnson CH, ed. SEER Program Coding and Staging Manual 2004, Revision 1. Bethesda, MD: National Cancer Institute, 2004. (NIH publication no. 04-5581).

[38] Aggravated prostate cancer included cases with tumor(s) defined as one of the following: distant stage or poorly differentiated (Gleason score 7-10), deadly prostate cancer, or Gleason ≥ 7.

Controls included white male applicators and were frequency-matched to the cases (2:1) by birth date (±1 year). Pesticide exposure was assessed through two self-administered questionnaires at study enrollment and shortly thereafter, and exposure was classified via intensity-weighted lifetime exposure days and categorized into non-exposed, low, and high exposure groups using the median as the cut point. Unconditional logistic regression was used to investigate the association between dicamba and prostate cancer, adjusting for state, age, and race. Among the total cases (n = 776) and controls (n = 1,444), 171 cases and 368 controls reported low dicamba exposure, 181 cases and 360 controls reported high dicamba exposure, and 324 cases and 573 controls respectively, reported no dicamba exposure. No evidence of a positive association was reported between dicamba exposure and prostate cancer among white male pesticide applicators in either the low or high exposure categories, with the non-exposed group as the referent (Low – OR = 0.78; 95% CI: 0.61, 1.00, with n = 171 exposed cases; High – OR = 0.82; 95% CI: 0.63, 1.05, with n = 181 exposed cases; p-trend = 0.318).

The overall quality of the study was ranked high based on the study quality criteria provided in the OPP Framework. The ranking was based on the general strengths of the AHS, including its prospective design, ability to identify cancer cases through linkage to cancer registries, and exposure assessment approach which examined cumulative lifetime exposure to dicamba.

- Lerro et al. (2020) investigated the association between dicamba exposure and several cancers including prostate cancer using data from the AHS prospective cohort that included additional cases and longer follow-up time than Samanic et al. (2006). The study population (n = 49,992) consisted of pesticide applicators living in Iowa and North Carolina who were enrolled in the AHS cohort and who reported information on dicamba exposure at enrollment and follow-up. Incident cancer cases were identified using Iowa and North Carolina state cancer registry files from enrollment (1993-1997) through December 2014 in North Carolina and December 2015 in Iowa. International Classification of Diseases for Oncology (ICD-0-2) codes were used to classify cancer sites. Dicamba exposure was assessed through the enrollment questionnaire (1993 – 1997) and the first follow-up interview five years after enrollment (1999 – 2005). Multiple imputation was used to estimate pesticide exposures at follow-up for individuals who did not complete the interview (n = 20,968, 37%). Poisson regression was used to calculate relative risks and 95% confidence intervals for each category of intensity-weighted days of dicamba use compared with no use, adjusting for age, race, sex, smoking, state, applicator type, education, imazethapyr use (Spearmen p = 0.49), and family history of cancer. Cumulative intensity-weighted days were categorized as no exposure or quartiles of exposure among all incident cancer cases for sites with > 20 exposed (no use, 5.0 – 449.5 days, 449.6 – 1260.0 days, 1260.1 – 3,698 days, >3,689 days) or based on the median, as no, low or high exposure for cancers and subtypes with 10–20 exposed cases (no use, 5.0 – 1,260.0 days, > 1,260.0 days). Among the 49,922 applicators, 26,412 (52.9%) reported dicamba exposure and among the 2,694 cases of prostate cancer, 1,360 reported dicamba exposure. No evidence of a significant positive association was reported for prostate cancer for any exposure category of cumulative intensity-weighted days of use (1.00 < RR < 1.07; all 95% CIs encompassed the null value of 1.0; with n = 372 – 406 exposed cases per category, p-trend > 0.05). For aggressive prostate cancer, no evidence of a significant positive association was reported for any exposure category of cumulative intensity-weighted days of use (0.95 < all RR < 1.11; all 95% CIs encompassed the null value of 1.0; with n = 212 – 241 exposed cases per category, p-trend > 0.05).

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The general strengths of the publication included the underlying prospective design of AHS, focus on U.S. agricultural populations, and availability of a U.S. registry to comprehensively identify cancer cases. Lerro et al. (2020) indirectly assessed dicamba exposure based on the AHS survey instrument. Limitations were noted including the fact that the authors did

not correct for/adjust for multiple comparison/multiple testing and that we would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported.

- Band et al. (2011) evaluated the potential association between pesticide exposure including dicamba, and prostate cancer among male pesticide applicators in a population-based case-control study in British Columbia, Canada. The study population included a subset of male cancer patients who previously enrolled in a case-control study. All participants were ascertained via the British Columbia Cancer Registry and all diagnoses were histologically confirmed. Prostate cancer cases were diagnosed between 1983 and 1985. Controls included men who were diagnosed with cancers other than prostate, lung or unknown primary site from 1983 through 1990 and were age-matched to the cases. Exposure was assessed using self-reported questionnaires provided at study enrollment that were completed at home and returned within 6-weeks and a Job Exposure Matrix was used to estimate lifetime cumulative exposure level by aggregating exposure over all jobs. Next-of-kin served as proxy respondents for deceased subjects (18.4% of cases and 17.2% of controls). Conditional logistic regression was used to calculated ORs and 95% CIs for the association between dicamba and prostate cancer, adjusting for smoking years, alcohol consumption, pipe years, education level, and proxy respondent. Among the 1,153 cases and 3,999 controls eligible for this analysis, 14 cases and 23 controls reported exposure to dicamba. No evidence of a significant positive association was reported between dicamba and prostate cancer (OR = 2.02; 95% CI: 0.98, 4.15; with n = 14 exposed cases) based on ever/never use. In an exposure-response analysis, where low and high categories of lifetime exposure were created by dividing the exposed controls into two equal halves, evidence of a moderately strong positive association was reported between dicamba exposure and prostate cancer in the high exposure category among a very small number of cases (OR = 2.70; 95% CI: 1.01, 7.20; with n = 8 exposed cases) with the no exposure as the referent and no evidence of a significant positive association was reported for the low exposure category (data not reported)

  The overall quality of the study was moderate based on the study quality criteria provided in the OPP Framework. Study strengths included the case-control study design, ascertainment of cases and controls from cancer registries, histological confirmation of diagnoses, and thoughtful selection of potential confounders and covariates. Use of cancer patients in both case and control groups may have decreased differential recall bias but may have increased risk of selection bias. Additional limitations included the potential for recall-bias due to inaccurate recall by proxy respondents (18.4% of the cases, 17.2% of the controls). We note also, the number of dicamba-exposed prostate cancer cases in the high exposure category (n = 8) was very small which severely restricts the ability to interpret with confidence the observed ORs as well as the ability to assess the exposure-response relationship.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and prostate cancer. Nine publications (Alavanja et al., 2003; Band et al., 2011; Barry et al., 2011; Barry et al., 2012; Koutros et al., 2011; Christensen et al., 2016; Koutros et al., 2013; Samanic et al., 2006; Lerro et al., 2020) examined the relationship between dicamba exposure and prostate cancer. Eight of the nine publications (Alavanja et al., 2003; Barry et al., 2011; Barry et al., 2012; Koutros et al., 2011; Christensen et al., 2016; Koutros et al., 2013; Samanic et al., 2006; Lerro et al., 2020) examined this association among the AHS prospective cohort population and all eight reported no evidence of a significant positive association between dicamba exposure and prostate cancer. The study quality for the AHS studies was either high or moderate and all benefited from the general strengths of the AHS including the prospective study design (three were

nested-case control), and linkage to cancer registries to ascertain cases. Study limitations were noted, namely potential for exposure misclassification and missing data among cases (~30% of the cases) and multiple comparisons without adjustment for multiple comparisons. The ninth publication, Band et al. (2011), evaluated the association between dicamba and prostate cancer in a population-based case-control study among farm workers in British Columbia, Canada. Evidence of a moderately strong positive association was reported in the high exposure category of the exposure-response analysis among a very small number of cases (n = 8). The study was moderate quality and limitations included selection bias, recall bias due to proxy respondents inaccurate recall of exposure. We note also, the number of dicamba-exposed prostate cancer cases in the high exposure category (n = 8) was very small.

Cancer of the Small Intestine

One publication (Lerro et al., 2020) examined the association between dicamba and cancer of the small intestine.

Lerro et al. (2020) investigated the association between dicamba exposure and several cancers including cancer of the small intestine using data from the AHS prospective cohort. The study population (n = 49,992) consisted of pesticide applicators living in Iowa and North Carolina who were enrolled in the AHS cohort and who reported information on dicamba exposure at enrollment and follow-up. Incident cancer cases were identified using Iowa and North Carolina state cancer registry files from enrollment (1993-1997) through December 2014 in North Carolina and December 2015 in Iowa. International Classification of Diseases for Oncology (ICD-0-2) codes were used to classify cancer sites. Dicamba exposure was assessed through the enrollment questionnaire (1993 – 1997) and the first follow-up interview five years after enrollment (1999 – 2005). Multiple imputation was used to estimate pesticide exposures at follow-up for individuals who did not complete the interview (n = 20, 968, 37%). Poisson regression was used to calculate relative risks and 95% confidence intervals for each category of intensity-weighted days of dicamba use compared with no use, adjusting for age, race, sex, smoking, state, applicator type, education, imazethapyr use (Spearmen p = 0.49), and family history of cancer. Cumulative intensity-weighted days were categorized as no exposure or quartiles of intensity-weighted days of exposure among all incident cancer cases for sites with > 20 exposed (no use, 5.0 – 449.5 days, 449.6 – 1260.0 days, 1260.1 – 3,698 days, >3,689 days) or based on the median, as no, low or high exposure for cancers and subtypes with 10–20 exposed cases (no use, 5.0 – 1,260.0 days, > 1,260.0 days). Among the 49,922 applicators, 26,412 (52.9%) reported dicamba exposure and among the 43 cases of stomach cancer, 23 reported dicamba exposure. No evidence of a significant positive association was reported for any exposure category (0.71 < RR < 1.17; all 95% CIs encompassed the null value of 1.0; with n = 5 – 8 exposed cases per exposure category; p-trend = 0.72), with the no exposure group as the referent, and no evidence of a significant exposure-response trend.

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The general strengths of the publication included the underlying prospective design of the AHS, focus on U.S. agricultural populations, and availability of a U.S. cancer registry to comprehensively identify cancer cases. Authors performed multiple comparisons however did not correct for multiple comparison. We would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a causal or clear associative relationship between dicamba exposure and cancer of the small intestine. One study (Lerro et al., 2020) examined the association between dicamba exposure and reported no evidence of a

significant positive association between dicamba intensity weighted lifetime days of dicamba use and cancer of the small intestine among farmers in the AHS prospective cohort in Iowa and North Carolina. The study was moderate quality and while the study had several strengths including the prospective study design, use of cancer registries to ascertain cases, and a validated questionnaire to assess pesticide exposure, several limitations were noted. In particular, over 40 different cancer analyses were performed and no adjustments for multiple comparisons were made. HED would expect several of the statistically significant results would no longer remain significant after appropriate adjustments that would account for the multiple comparisons performed. Additionally, we noted several concerns with respect to confounder adjustments that suggest there may be issues with sample size and/or the statistical model/statistical analysis that may affect the reliability of the analysis.

Soft Tissue Sarcoma

Two publications (Pahwa et al., 2006; Pahwa et al., 2011) examined the association between dicamba and soft tissue sarcoma (STS).

- Pahwa et al. (2006) investigated the potential association between dicamba and STS among men living in Canada using data from the population-based case-control study Cross-Canada Study of Pesticides and Health Study (CCSPH). The study population included males ≥ 19 years old who lived in one of six Canadian provinces and completed a postal questionnaire. Deceased participants were excluded from this analysis. Cases of STS included those adult males diagnosed between September 1991 to December 1994 and were ascertained via provincial cancer registries or hospital ascertainment (Quebec only). Cases were validated by a pathologist who reviewed pathology slides. Controls were randomly selected males from either health insurance records, telephone directories (Ontario) or voters lists (British Columbia), who resided in the same Canadian provinces as cases, and were matched to cases via age (± 2 years). A postal questionnaire was mailed to cases and controls to assess pesticide exposure, and follow-up telephone interviews regarding detailed pesticide use were conducted for each subject who reported more than 10 hours per year of pesticide use. The response rates for cases and controls was 67.1% and 48.0%, respectively.[39] Exposure to dicamba included pesticides with dicamba as the main active ingredient and mixtures of herbicides including dicamba as one of multiple active ingredients. Conditional logistic regression was used to calculate ORs and 95% CIs for the association between dicamba and dicamba containing mixtures and STS, adjusting for age and province of residence. Among the total STS cases (n = 357), 40 reported exposure to any dicamba containing herbicide, and 131 of the 1,506 controls reported exposure to any dicamba containing herbicide. No evidence of a significant positive association was reported for any dicamba exposure (including mixtures)[40] and STS (OR = 1.30; 95% CI: 0.87, 1.92; with n = 40 exposed cases and n = 131 exposed controls). An additional analysis that was limited to farm workers/dwellers only, reported no evidence of a positive association between exposure to dicamba-containing herbicides and STS (OR = 0.99; 95% CI: 0.58, 1.67 with n = 23 exposed cases, n = 97 exposed controls).

  The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths included the study design, age matching the cases to the controls, case ascertainment, and exposure assessment. Potential recall bias was considered a

Commented [JE14]: double check these results are not mixed with PAHWA et al. 2011

[39] McDuffie, H. H., Pahwa, P., Robson, D., Dosman, J. A., Fincham, S., Spinelli, J. J., & McLaughlin, J. R. (2005). Insect repellents, phenoxyherbicide exposure, and non-Hodgkin's lymphoma. J Occup Environ Med, 47(8), 806-816. doi:10.1097/01.jom.0000167260.80687.78

[40] For any dicamba exposure, authors included exposures to dicamba as the sole active ingredient and to products that were mixtures that contained active ingredients in addition to dicamba such as: dicamba and glyphosate; and dicamba, 2,4-D, and mecoprop.

limitation, as the cases living with the outcome may have remembered certain past exposures more accurately than the controls. Another limitation of the study was the response rate to the mailed questionnaires. Only 67.1% of the contacted cases and 48% of the contacted controls responded to the questionnaire and were included in the analysis. There may have been differences between those who responded and those who did not respond.

- In an additional analysis using the same study population as Pahwa et al. (2006), Pahwa et al. (2011) investigated the potential association between dicamba[41] exposure and STS among men in the CCSPH, while taking into account the effects of medical history on the potential association. Conditional logistic regression was used to calculate ORs and 95% CIs for the association between individual pesticide exposures including dicamba and STS, adjusted for age and province of residence and also relevant medical history variables[42] including family history of cancer. Among the total STS cases (n = 357) and population controls (n = 1,506), 40 (11.2%) cases and 132 (8.7%) controls reported exposure to dicamba or dicamba containing mixtures and 15 (4.2%) cases and 50 (3.3%) controls reported exposure to pesticide products containing dicamba as the sole active ingredient. No evidence of a significant positive association was reported between dicamba exposure as main active ingredient and STS among men (OR = 1.31; 95% CI: 0.61, 2.82; with n = 15 exposed cases), when further adjusted for medical history variables. Similarly, when all dicamba exposures (dicamba as sole active ingredient and dicamba containing mixtures of herbicides) were considered, no evidence of a significant positive association was reported between exposure to dicamba and mixtures with dicamba and other active ingredients combined and STS among men (OR = 1.26; 95% CI: 0.84, 1.90; with n = 40 exposed cases).

  The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths included the study design, age matching the cases to the controls, case ascertainment, and exposure assessment. Potential recall bias was considered a limitation, as the cases living with the outcome may have remembered certain past exposures more accurately than the controls. Another limitation of the study was the response rate to the mailed questionnaires. Only 67.1% of the contacted cases and 48% of the contacted controls responded to the questionnaire and were included in the analysis. There may have been differences between those who responded and those who did not respond.

EPA Conclusion

Overall, there is insufficient epidemiological evidence at this time to conclude that there is a causal or clear associative relationship between dicamba exposure and STS. This determination is based on two publications (Pahwa et al., 2006; Pahwa et al., 2011) that investigated the potential association between exposure to dicamba and dicamba containing herbicide mixtures and soft tissue sarcoma (STS), in case-control analysis of participants of the Cross-Canada Study of Pesticides and Health Study while considering exposure to DEET (Pahwa et al., 2006) and medical and familial history of cancer (Pahwa et al., 2011) and reported no evidence of a significant positive association between dicamba exposure and STS based on ever exposure. Both studies were ranked moderate quality based on the study quality criteria provided in the OPP Framework. Study strengths included the study design, age matching the cases to the controls, case ascertainment, and exposure assessment. Potential recall bias was considered a

[41] In Pahwa et al. (2011), "dicamba as a major chemical class" includes products that contain dicamba as the sole active ingredient such as Banvel and Target, and mixtures of dicamba with other active ingredients such as dicamba and glyphosate (Rustler) and dicamba, 2,4-D, and mecoprop (Dynel DS, Killex).
[42] Medical history variables included: mononucleosis, whooping cough, history of measles, rheumatoid arthritis, and a positive family history of cancer in a first-degree relative.

limitation, as the cases living with the outcome may have remembered certain past exposures more accurately than the controls. Another limitation of the study was the response rate to the mailed questionnaires. Only 67.1% of the contacted cases and 48% of the contacted controls responded to the questionnaire and were included in the analysis. There may have been differences between those who responded and those who did not respond.

Stomach Cancer

Two publications (Lee et al., 2004; Lerro et al., 2020) examined the association between dicamba and stomach cancer.

- Lee et al. (2004) investigated the association between farming and agricultural pesticide use, including dicamba, and stomach and esophageal cancers in the Nebraska Health Study II, a case-control study of adults in eastern Nebraska. The study population included white residents of eastern Nebraska, ≥21 years old. Cases of incident stomach and esophageal adenocarcinoma were identified using the Nebraska Cancer Registry (1988 – 1990) and discharge and pathology records from 14 participating hospitals Nebraska. Controls for the current study were randomly selected from the control group of a previous study covering the same base population investigating lymphohematopoietic cancers (<65 years – random digit dialing, ≥65 years – Medicare files, for deceased cases – Nebraska mortality records) and were frequency matched by age, gender, and vital status to the combined distribution of the glioma, stomach, and esophagus cancer cases. Demographic, medical and family history, occupational, and, pesticide exposure information (for those who lived or worked on farm) was collected via telephone interview conducted during 1992-1994. Pesticide exposure information was limited to use prior to 1985, the time period of the previous study. Interviews were conducted for 170 stomach cancer cases, 137 esophageal cancer cases and 502 controls, however most interviews were conducted via proxy (76% of esophageal adenocarcinoma cases, 80% of stomach cancer cases, 61% of controls) who were primarily spouses or other primary relatives. Unconditional logistic regression was used to calculate ORs and 95% CIs for farming activity and for individual pesticide use, adjusted for age and gender, with the non-farmers as a reference group. Among the 170 stomach cancer cases and 502 controls included in the final analysis, 4 stomach cancer cases and 35 controls reported dicamba exposure. No evidence of a positive association was reported for dicamba ever use and stomach cancer among farmers in Nebraska, among a very small number of cases (OR = 0.30; 95% CI: 0.10, 1.00; with n = 4 exposed cases).

  The quality of the study was ranked low quality based on the study quality criteria provided in the OPP framework. The study had several important limitations related to its design, exposure assessment approach, statistical analysis, and ability to control for confounding. With regard to study design, Lee et al. (2005) used a case-control approach and may have introduced selection bias when recruiting their control group. Differences between the results for the self-reporting respondents and the proxy respondents illustrate the possible problem, as the control groups for each of these respondents were constructed differently and each could be biased in a different way. In the analysis, the reference group for the statistical tests was non-farmers, even though the pesticide use questions were not asked of non-farmers. As a result, the results for pesticides are confounded with farmer versus non-farmers and control groups with different proportions of farmers will result in different statistical results. The use of respondent-reported dicamba use to ascertain exposure introduced further uncertainty because it is not possible to attribute the increased odds of glioma to dicamba exposure alone. In particular, the self-reporting and proxy respondents have different levels of knowledge about pesticide use and possibly different motives for responding. Moreover, self-reported exposure assessment is likely to be subject to differential misclassification because study participants may incorrectly recall previous pesticide usage. In addition to these limitations, findings on dicamba

are based on only 4 exposed cases which severely restricts the ability to interpret with confidence the observed odds ratios as well as the ability to assess the exposure-response relationship.

- Lerro et al. (2020) investigated the association between dicamba exposure and several cancers including stomach cancer using data from the AHS prospective cohort. The study population (n = 49,992) consisted of pesticide applicators living in Iowa and North Carolina who were enrolled in the AHS cohort and who reported information on dicamba exposure at enrollment and follow-up. Incident cancer cases were identified using Iowa and North Carolina state cancer registry files from enrollment (1993-1997) through December 2014 in North Carolina and December 2015 in Iowa. International Classification of Diseases for Oncology (ICD-0-2) codes were used to classify cancer sites. Dicamba exposure was assessed through the enrollment questionnaire (1993 – 1997) and the first follow-up interview five years after enrollment (1999 – 2005). Multiple imputation was used to estimate pesticide exposures at follow-up for individuals who did not complete the interview (n = 20, 968, 37%). Poisson regression was used to calculate relative risks and 95% confidence intervals for each category of intensity-weighted days of dicamba use compared with no use, adjusting for age, race, sex, smoking, state, applicator type, education, imazethapyr use (Spearmen p = 0.49), and family history of cancer. The analysis for stomach cancer was also adjusted for alcohol consumption and BMI. Cumulative intensity-weighted days were categorized as no exposure or quartiles of intensity-weighted days of exposure among all incident cancer cases for sites with > 20 exposed (no use, 5.0 – 449.5 days, 449.6 – 1260.0 days, 1260.1 – 3,698 days, >3,689 days) or based on the median, as no, low or high exposure for cancers and subtypes with 10–20 exposed cases (no use, 5.0 – 1,260.0 days, > 1,260.0 days). Among the 49,922 applicators, 26,412 (52.9%) reported dicamba exposure and among the 107 cases of stomach cancer, 47 reported dicamba exposure. No evidence of a positive association was reported for any exposure category (0.56 < RR < 0.95; all 95% CIs encompassed the null value of 1.0; with n = 8 – 15 exposed cases per exposure category; p-trend = 0.45), with the no exposure group as the referent, and no evidence of a significant exposure-response trend.

  The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The general strengths of the publication included the underlying prospective design of the AHS, focus on U.S. agricultural populations, and availability of a U.S. cancer registry to comprehensively identify cancer cases. Authors performed multiple comparisons however did not correct for multiple comparison. We would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported.

EPA Conclusion

Overall, there is *no epidemiological evidence* at this time to conclude that there is a causal or clear associative relationship between dicamba exposure and stomach cancer. Two studies (Lee et al., 2004; Lerro et al., 2020) examined the association between dicamba exposure. Lee et al. (2004) reported no evidence of a positive association among farmers in Nebraska and was ranked low quality due to several limitations with the study design. Lerro et al. (2020) reported no evidence of a positive association between dicamba intensity weighted lifetime days of dicamba use and stomach cancer among the large AHS prospective cohort in Iowa and North Carolina. Lerro et al. (2020) was deemed moderate quality for regulatory purposes and while the outcome and exposure assessments were strong, a notable limitation was the multiple comparisons without statistical correction.

Testicular Cancer

One publication (Lerro et al., 2020) examined the association between dicamba and testicular cancer.

Lerro et al. (2020) investigated the association between dicamba exposure and several cancers including testicular cancer using data from the AHS prospective cohort. The study population (n = 49,992) consisted of pesticide applicators living in Iowa and North Carolina who were enrolled in the AHS cohort and who reported information on dicamba exposure at enrollment and follow-up. Incident cancer cases were identified using Iowa and North Carolina state cancer registry files from enrollment (1993-1997) through December 2014 in North Carolina and December 2015 in Iowa. International Classification of Diseases for Oncology (ICD-0-2) codes were used to classify cancer sites. Dicamba exposure was assessed through the enrollment questionnaire (1993 – 1997) and the first follow-up interview five years after enrollment (1999 – 2005). Multiple imputation was used to estimate pesticide exposures at follow-up for individuals who did not complete the interview (n = 20, 968, 37%). Poisson regression was used to calculate relative risks and 95% confidence intervals for each category of intensity-weighted days of dicamba use compared with no use, adjusting for age, race, sex, smoking, state, applicator type, education, imazethapyr use (Spearmen p = 0.49), and family history of cancer. Cumulative intensity-weighted days were categorized as no exposure or quartiles of intensity-weighted days of exposure among all incident cancer cases for sites with > 20 exposed (no use, 5.0 – 449.5 days, 449.6 – 1260.0 days, 1260.1 – 3,698 days, >3,689 days) or based on the median, as no, low or high exposure for cancers and subtypes with 10–20 exposed cases (no use, 5.0 – 1,260.0 days, > 1,260.0 days). Among the 49,922 applicators, 26,412 (52.9%) reported dicamba exposure and among the 49 cases of testicular cancer, 23 cases reported dicamba exposure. No evidence of a positive association was reported for any exposure category (0.69 < RR < 1.00; all 95% CIs encompassed the null value of 1.0; with n = 5 – 7 exposed cases per exposure category; p-trend = 0.71), with the no exposure group as the referent, and no evidence of a significant exposure-response trend.

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The general strengths of the publication included the underlying prospective design of the AHS, focus on U.S. agricultural populations, and availability of a U.S. cancer registry to comprehensively identify cancer cases. Authors performed multiple comparisons however did not correct for multiple comparison. We would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported.

EPA Conclusion

Overall, there is *no epidemiological evidence* at this time to conclude that there is a causal or clear associative relationship between dicamba exposure and lip cancer. One study (Lerro et al., 2020) examined the association between dicamba exposure and lip cancer. Lerro et al. (2020) reported no evidence of a significant positive association between dicamba intensity weighted lifetime days of dicamba use and lip cancer among the large AHS prospective cohort in Iowa and North Carolina. Lerro et al. (2020) was deemed moderate quality for regulatory purposes and while the outcome and exposure assessments were strong, a notable limitation was the multiple comparisons without statistical correction.

Tongue Cancer

One publication (Lerro et al., 2020) examined the association between dicamba and lip cancer.

Lerro et al. (2020) investigated the association between dicamba exposure and several cancers including tongue cancer using data from the AHS prospective cohort. The study population (n = 49,992) consisted

of pesticide applicators living in Iowa and North Carolina who were enrolled in the AHS cohort and who reported information on dicamba exposure at enrollment and follow-up. Incident cancer cases were identified using Iowa and North Carolina state cancer registry files from enrollment (1993-1997) through December 2014 in North Carolina and December 2015 in Iowa. International Classification of Diseases for Oncology (ICD-0-2) codes were used to classify cancer sites. Dicamba exposure was assessed through the enrollment questionnaire (1993 – 1997) and the first follow-up interview five years after enrollment (1999 – 2005). Multiple imputation was used to estimate pesticide exposures at follow-up for individuals who did not complete the interview (n = 20, 968, 37%). Poisson regression was used to calculate relative risks and 95% confidence intervals for each category of intensity-weighted days of dicamba use compared with no use, adjusting for age, race, sex, smoking, state, applicator type, education, imazethapyr use (Spearmen p = 0.49), and family history of cancer. The analysis for tongue cancer was also adjusted for pack-years smoked (tertiles by smoking status) and non-combustible tobacco use. Cumulative intensity-weighted days were categorized as no exposure or quartiles of intensity-weighted days of exposure among all incident cancer cases for sites with > 20 exposed (no use, 5.0 – 449.5 days, 449.6 – 1260.0 days, 1260.1 – 3,698 days, >3,689 days) or based on the median, as no, low or high exposure for cancers and subtypes with 10–20 exposed cases (no use, 5.0 – 1,260.0 days, > 1,260.0 days). Among the 49,922 applicators, 26,412 (52.9%) reported dicamba exposure and among the 34 cases of tongue cancer, 16 reported dicamba exposure. No evidence of a positive association was reported for any exposure category ($0.50 < RR < 0.93$; all 95% CIs encompassed the null value of 1.0; with n = 5 – 10 exposed cases per exposure category; p-trend = 0.17), with the no exposure group as the referent, and no evidence of a significant exposure-response trend.

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The general strengths of the publication included the underlying prospective design of the AHS, focus on U.S. agricultural populations, and availability of a U.S. cancer registry to comprehensively identify cancer cases. Authors performed multiple comparisons however did not correct for multiple comparison. We would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported.

EPA Conclusion

Overall, there is *no epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and tongue cancer. One study (Lerro et al., 2020) examined the association between dicamba exposure and tongue cancer and reported no evidence of a positive association between dicamba intensity-weighted lifetime days of dicamba use and tongue cancer among the large AHS prospective cohort in Iowa and North Carolina. The study was moderate and while the outcome and exposure assessments were strong, limitations included the multiple comparisons without statistical correction and the potential for incomplete confounder adjustment.

Tonsil Cancer

One publication (Lerro et al., 2020) examined the association between dicamba and tonsil cancer.

Lerro et al. (2020) investigated the association between dicamba exposure and several cancers, including tonsil cancer, using data from the AHS prospective cohort. The study population (n = 49,992) consisted of pesticide applicators living in Iowa and North Carolina who were enrolled in the AHS cohort and who reported information on dicamba exposure at enrollment and follow-up. Incident cancer cases were identified using Iowa and North Carolina state cancer registry files from enrollment (1993-1997) through December 2014 in North Carolina and December 2015 in Iowa. International Classification of Diseases for Oncology (ICD-0-2) codes were used to classify cancer sites. Dicamba exposure was assessed through

the enrollment questionnaire (1993 – 1997) and the first follow-up interview five years after enrollment (1999 – 2005). Multiple imputation was used to estimate pesticide exposures at follow-up for individuals who did not complete the interview (n = 20, 968, 37%). Poisson regression was used to calculate relative risks and 95% confidence intervals for each category of intensity-weighted days of dicamba use compared with no use, adjusting for age, race, sex, smoking, state, applicator type, education, imazethapyr use (Spearmen p = 0.49), and family history of cancer. The analysis for tonsil cancer was also adjusted for pack years smoking. Cumulative intensity-weighted days were categorized as no exposure or quartiles of intensity-weighted days of exposure among all incident cancer cases for sites with > 20 exposed (no use, 5.0 – 449.5 days, 449.6 – 1260.0 days, 1260.1 – 3,698 days, >3,689 days) or based on the median, as no, low or high exposure for cancers and subtypes with 10–20 exposed cases (no use, 5.0 – 1,260.0 days, > 1,260.0 days). Among the 49,922 applicators, 26,412 (52.9%) reported dicamba exposure and among the 25 cases of tonsil cancer, 16 reported dicamba exposure. Evidence of a positive association was reported for the low exposure category if intensity weighted days of dicamba exposure and tonsil cancer among a small number of cases (*5.0 – 1,260.0 days* – RR = 1.86; 95% CI: 1.19, 2.88; with n = 11 exposed cases), with the no exposure group as the referent. No evidence of a positive association was reported for the high exposure category among a very small number of exposed cases (*>1,260 days* – RR = 0.64; 95% CI: 0.39, 1.04; with n = 5 exposed cases), with the no exposure group as the referent, and evidence of a significant exposure-response trend (p-trend < 0.001).

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The general strengths of the publication included the underlying prospective design of the AHS, focus on U.S. agricultural populations, and availability of a U.S. cancer registry to comprehensively identify cancer cases. Authors performed multiple comparisons however did not correct for multiple comparison. We would expect several statistically significant results to go away after such statistical adjustment. Results from the ever/never use analysis were not reported. We note the small number of dicamba exposed cases which restricts the ability to interpret with confidence the observed rate ratios.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and tonsil cancer. One study (Lerro et al., 2020) examined the association between dicamba exposure and tonsil cancer among the AHS prospective cohort and reported evidence of a positive association in the low exposure category and no evidence of a positive association in the high exposure category. Additionally, evidence of a significant exposure-response trend (p-trend < 0.001) was reported, with the no exposure group as the referent. This finding was reported among a small number of dicamba-exposed cases (n = 11). The study was moderate and while the outcome and exposure assessments were strong, limitations included the multiple comparisons without statistical correction and we noted several concerns with respect to confounder adjustments that suggest there may be issues with samples size and/or the statistical model/statistical analysis. Also, the reported association between dicamba exposure and tonsil cancer is a first time (exploratory) finding and AHS practice is to require a second follow-on confirmatory finding to begin to consider making any conclusions. This latter point is acknowledged by the study authors who conclude that future epidemiologic work on dicamba should focus on replication of their study findings.

3.6.2 Noncarcinogenic Health Outcomes

For noncarcinogenic health outcomes, EPA conducted a review of 45 publications which investigated the relationship between dicamba exposure and 26 non-carcinogenic adverse health effects including allergies, amyotrophic lateral sclerosis, autoimmune disease, rheumatoid arthritis, birth defects, birthweight, depression, diabetes, dream enacting behaviors, end stage renal disease, eye disorders, fatal

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injury, monoclonal gammopathy of undetermined significance, myocardial infarction, olfactory impairment, Parkinson's disease, respiratory effects (including asthma, chronic bronchitis, rhinitis, wheeze), sleep apnea, stroke, suicide, and thyroid disease (including hyperthyroid, hypothyroid, and other thyroid disease). The 45 studies for these health outcomes are described below.

Allergies

One publication (Weselak et al., 2007) examined the association between dicamba exposure and allergies or hayfever among children.

Weselak et al. (2007) investigated the potential association between pesticide exposures including dicamba among farm couples and allergies in their offspring. The study population was part of the Ontario Farm Family Health Study (OFFHS). Weselak et al. (2007) analyzed farm couple's various exposures during pregnancy including pesticide exposure and respiratory effects (asthma bronchitis, persistent cough or bronchitis) and hay fever or allergies. Three questionnaires were mailed to participants, one for each the husband, wife, and the farm pesticide applicator if different form either the husband or wife. Wives were asked to report a full reproductive history of their first five pregnancies and their health outcome, as well as if a doctor had ever told them that their child had any of the following health conditions: asthma, chronic bronchitis or cough, and hayfever or allergies. For the exposure assessment, data was pooled from questionnaires completed by the wife and the husband, in addition to a farm applicator if separate from the husband or wife. Exposure questionnaires reported on exposure details regarding pesticide applications, with the addition of a direct chemical activities assessment. Logistic regression was used to calculate ORs and corresponding 95% CIs for the association between dicamba exposure and the mentioned health conditions, adjusting for specific covariates within each analysis. Dicamba models were adjusted for Among the total number of offspring (n = 3,405) in this study, parental exposure to dicamba during pregnancy (month of conception up to the month of delivery) was reported for 282 of the total 2,243 exposed offspring and of those exposed to dicamba, 10 reported asthma, 9 reported chronic bronchitis or cough, and 19 reported hayfever or allergies. No evidence of a positive association was reported for dicamba exposure during pregnancy and hayfever and allergies in offspring (Crude OR = 0.67; 95% CI: 0.39, 1.14; with n = 19 exposed cases). When adjusted for child's age at time of questionnaire, fathers age at conception, and maternal weight gain during pregnancy, covariates that when added to the crude model changed the exposure OR by 10% or more, no evidence of a significant positive association was reported (OR = 1.51; 95% CI: 0.77, 2.93; with n=19 exposed cases). When offspring were stratified by gender (male, female), no evidence of a significant positive association was reported between dicamba exposure during pregnancy and hayfever or allergies among male offspring (OR = 1.74; 95% CI: 0.74, 4.11; with n = 12 exposed cases) or among female offspring (OR = 1.04; 95% CI: 0.35, 3.09; with n = 7 exposed cases), among a small number of cases.

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Overall Weselak et al. (2007) was considered moderate quality based on the Framework. Despite being a population-based cohort study, exposure and outcome information were both gathered retrospectively by self-report without any corroboration pesticide use data or confirmation of outcome by medical record abstraction. Since dosing information was not provided in this study, the degree of exposure for each study subject was unknown and could have potentially led to misclassification. Also, because several couples included within the study were reporting on several past pesticide exposures and past pregnancies, and assuming some pregnancies led to poor outcomes (i.e. abortions), recall bias could have occurred and ultimately affected the woman's behavior for future pregnancies and couples' memory of pesticide exposure. Lastly, a small number of exposed cases were observed.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and allergy. One study (Weselak et al., 2007) examined the association between dicamba exposure during pregnancy and allergy among the particpants of the Ontario Farm Family Health Study, a population-based retrospective cohort study conducted in Canada. Weselak et al. (2007) reported no evidence of a significant positive association between dicamba exposure during pregnancy and allergy or hayfever in offspring, among a small number of cases. We note the very small number of dicamba exposed cases which restricts the ability to interpret with confidence the observed odds ratios. The study was ranked moderate quality and limitations included the potential for recall bias, exposure misclassification, and outcome misclassification.

Amyotrophic Lateral Sclerosis

The association between dicamba exposure and Amyotrophic Lateral Sclerosis (ALS) was evaluated in one AHS study (Kamel et al., 2012) described below.

Kamel et al. (2012) investigated the association between pesticide exposure, including dicamba, and ALS among private pesticide applicators and their spouses in the AHS prospective cohort. Cases of ALS were identified using vital statistics data in Iowa and North Carolina and the National Death Index from enrollment through February 7, 2010 and were defined as having ALS listed as an underlying or contributing cause of death on the death certificate. Pesticide exposure (ever use and days of use) was self-reported via questionnaire completed at study enrollment (1993 – 1997) and shortly thereafter. Authors compared the 41 cases of ALS to the rest of the AHS cohort (84,689) and unconditional logistic regression was used to calculate ORs and 95% CIs for the association between dicamba exposure and ALS, adjusting for age and gender.[43] Among the 41 cases and 84,689 controls, 12 (32%) cases and 24,332 (31%) controls reported dicamba exposure. No evidence of a significant positive association was reported between dicamba exposure and ALS among a small number of cases (OR = 1.40; 95% CI: 0.60, 3.10; with n = 12 exposed cases).

The quality of the study was ranked high based on the study quality criteria provided in the OPP Framework. As part of the AHS, this study benefited from the strengths of the AHS study cohort including the prospective cohort study design, case ascertainment, and the exposure assessment.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and ALS. One study (Kamel et al., 2012) examined the association between dicamba exposure among AHS participants and ALS and reported no evidence of a significant positive association, among a small number of cases. The quality of the study was ranked high and strengths included the prospective cohort study design, case ascertainment, and exposure assessment.

Autoimmune Disease

Three studies examined the effects of dicamba exposure and autoimmune disease including antinuclear antibodies (markers of autoimmune disease) and rheumatoid arthritis.

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[43] ALS incidence is greater in men and risk of ALS increases with increased age.

Antinuclear Antibodies – markers of autoimmune disease

One study, Parks et al., 2019, examined the association between dicamba exposure and the risk of developing systemic autoimmunity (autoimmune disease).

Parks et al., 2019 investigated the association between pesticide exposure, including dicamba and autoimmune disease among pesticide applicators enrolled in the Biomarkers of Exposure and Effect in Agriculture (BEEA) study within the AHS, a large prospective cohort of farmers from Iowa and North Carolina. The study population included male private pesticide applicators living in Iowa or North Carolina who were enrolled in the AHS. Additionally, eligible participants of the BEEA were ≥ 50 years of age, completed the AHS enrollment questionnaire and the two follow-up interviews (1999-2003 and 2005-2010), had never been diagnosed with cancer other than non-melanoma skin cancer, and did not report a doctor diagnosis of systemic autoimmune disease at AHS enrollment. Among the 699 male private pesticide applicators enrolled in the BEEA study between June 2010 and September 2013, 668 were included in this analysis and of those, 110 reported exposure to dicamba. Markers of autoimmune disease, including Anti-nuclear antibodies (ANA), extractable nuclear antibodies (ENA) and anti-dsDNA antibodies, were detected in serum extracted from non-fasting blood specimens of study participants. Samples were collected in participant's home and were shipped cold via overnight delivery before processing and storage at -80C. ANA was measured using immunofluorescence assay using a standardized protocol in a rheumatology laboratory experienced in high-throughput testing. Samples positive for ANA were subsequently tested for ENA and anti-dsDNA antibodies. ANA positivity was based on highest reading observed and was divided into three exclusive categories of positivity to indicate an increasing threshold for ANA positivity: "Any ANA" (≥ 1:80 dilution at 2+ intensity reading), "Moderate-higher" (≥ 1:80 dilution at 3/4+ intensity reading), and "Higher" (≥ 1:160 dilution at 3/4+ intensity reading.). Pesticide exposure was assessed from pesticide use data reported on enrollment questionnaires (1993 – 1997), during the two follow-up interviews (1999 – 2003 and 2005 – 2010), and at BEEA enrollment to determine lifetime use of dicamba. Among the 665 study participants, 478 reported exposure to dicamba and of these, 210 had positive ANA level and 286 with dicamba use had a negative result. The association between lifetime use of dicamba reported at enrollment and ANA positivity level (Any ANA, Moderate-higher, Higher) compared to those with no detectable ANA was assessed using three separate multivariable logistic regression models to determine ORs and 95% CIs adjusted for covariates measured at BEEA interview including: age, BMI, state, ever smoked, spring or summer season of blood draw, and use of agricultural pesticides in the past 12 months. No evidence of a significant positive association was reported for lifetime use of dicamba and any of the three ANA categories (*Any ANA* – OR = 1.11; 95% CI: 0.75, 1.64; with n = 99 exposed cases; *Moderate-higher ANA* – OR = 1.33; 95% CI: 0.79, 2.22; with n = 58 exposed cases; *Higher ANA* – OR = 1.33; 95% CI: 0.64, 2.75; with n=53 exposed cases), with the no detectable ANA group as the referent.

In an additional analysis authors examined the association between dicamba exposure and the presence of ENA or anti-dsDNA autoantibodies compared to those with no ANA level detected, adjusted for age. Eleven (73%) of the 15 cases with ENA/anti-dsDNA detected and 286 (69%) of the 386 with no ANA level detected reported dicamba ever exposure. No evidence of a significant positive association was reported for the association between dicamba ever exposure and detection of ENA/anti-dsDNA autoantibodies among participants (OR = 1.78; 95% CI: 0.37, 8.55; with n = 11 dicamba exposed cases of ENA/anti-dsDNA out of 15, and n = 286 dicamba exposed participants with no detectable ANA out of 386; p-value 0.474).

The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The study benefited from the general strengths of the AHS, including the prospective cohort study design and the exposure assessment approach which examined cumulative lifetime exposure to dicamba. Additionally, the outcome of autoimmune disease markers ANA and ENA/anti-dsDNA were

detected using laboratory methods rather than via self-report by the participant. A noted limitation of the study is the ambiguity around the temporality of the exposure and the outcome. It is unclear if ANA developed after exposure to pesticides or before or whether ANA appeared in the past but was no longer present at time of blood sample collection.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and autoimmune disease. One study (Parks et al., 2019) examined the association between dicamba exposure among agricultural workers and risk of autoimmune disease among a subset of the AHS prospective cohort population; those enrolled in the Biomarkers of Exposure and Effect in Agriculture sub cohort. Parks et al. (2019) reported no evidence of a significant positive association between dicamba exposure and biomarkers for autoimmune disease. The quality of the study was ranked moderate and benefited from the general strengths of the AHS, including the prospective cohort study design and the exposure assessment approach which examined cumulative lifetime exposure to dicamba. A noted limitation of the study is the ambiguity around the temporality of the exposure and the outcome. It is unclear if ANA developed after exposure to pesticides or before or whether ANA appeared in the past but was no longer present at time of blood sample collection.

Rheumatoid Arthritis

The association between dicamba exposure and rheumatoid arthritis (RA) was evaluated in two publications (Parks et al., 2016, Meyer et al., 2017) described below.

- Parks et al. (2016) investigated the association of dicamba and other pesticide exposures and RA among wives of pesticide applicators in the AHS. Using a cohort study design, women (n = 24,293) self-reported physician-diagnosed RA and pesticide use through questionnaires completed at enrollment (Phase 1: 1993 and 1997) for prevalent RA cases and follow up (Phase 2, 1998–2003; Phase 3, 2005–2010) for incident RA cases. Cases of self-reported RA were classified as confirmed if the self-reported RA was supported by physician data or probable if participants self-reported taking of medications specific to RA on a screening questionnaire.[44] Logistic regression was used to estimate ORs and CIs, adjusting for age, state, and pack-years smoking. Of the 271 total cases of RA among study participants, seven (3%) reported exposure to dicamba, and of the 129 incident cases of RA, 4 (3%) reported dicamba exposure. Of the 23,570 noncases with complete data, 949 (4%) reported dicamba exposure. Results suggested no evidence of a positive association between dicamba exposure and all (incident and prevalent) RA cases (OR = 0.68; 95% CI: 0.32, 1.50 for total RA). Incident RA ORs were not calculated because there were less than five incident cases of RA that reported exposure to dicamba.

  The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The ranking was based on the general strengths of the AHS, including its cohort design. Study limitations included the use of proxy respondents (~22 filled out screening questionnaires) and the self-reported outcomes among several of the study participants. Although study authors indicated that some RA cases were physician-confirmed during later phases of the study, some RA cases were self-reported earlier on in the study and were contacted at a later date to provide additional data via questionnaire to validate their RA case status. This self-validating method is not the same as the cases

[44] The study authors reported that identifying the probable cases (those who self-reported taking of medications specific to RA) provided "more power to focus on incident cases, which may minimize the influence of recall bias or healthy worker effect." (Parks et al. 2016)

who were ascertained by a physician, and likely led to bias and exposure misclassification. Additionally, different methods were used to collect pesticide use information. Participants were either mailed questionnaires or interviewed by telephone; participants who were interviewed by phone were prompted with a list of pesticide names, and these participants may have remembered their pesticide exposures more accurately than participants (those whom completed the mailed questionnaires) whom were not prompted with pesticide names. Lastly, we note a very small number of total RA cases and incident RA cases ($n \leq 10$) reported for dicamba in the analysis between dicamba exposure and RA.

- Meyer et al. (2017) investigated the potential association between exposure to pesticides including dicamba and RA in male pesticide applicators in the AHS. The study population included male pesticide applicators enrolled in the AHS between 1993 – 1997, who completed at least one follow-up questionnaire (Phase 2: 1999 – 2003, Phase 3: 2005 – 2010, Phase 4: 2013 – 2015). Incident RA cases were identified either through self-reported use of disease-modifying antirheumatic drugs, use of steroids for RA, or self-reported RA diagnosis by a rheumatologist on the follow-up questionnaires.[45] Eligible cases who reported RA on the follow-up interview were screened by telephone to confirm their diagnosis and to confirm use of disease-modifying antirheumatic drugs. Noncases included pesticide applicators who did not report RA and had complete covariate data. Pesticide exposure was self-reported on the enrollment questionnaires and used to determine ever use and cumulative lifetime days of use for specific pesticides including dicamba. The association between dicamba exposure (ever use, lifetime use, and IWLD of use) vs. no use and RA was estimated using logistic regression models adjusted for age, pack-years smoking, education, and state of enrollment. Exposure-response analysis was only conducted for those pesticides with ≥ 20 exposed cases and an OR ≥ 1.20 for ever use. Covariates were selected based on hypothesized or observed associations with RA and pesticide use overall, and covariates included in the final model were confirmed using selection by stepwise regression. Among the total probable incident RA cases (n = 220) and noncases (n = 26,134), 92 (46%) cases and 13,402 (55%) non-cases reported exposure to dicamba, based on ever/never use. No evidence of a positive association was reported between dicamba exposure and incident RA cases among male pesticide applicators (OR = 0.90; 95% CI: 0.65, 1.25; with n = 92 exposed cases). Exposure-response analysis was not conducted for dicamba because the ever use OR was not ≥ 1.20.

  The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The study benefited from the general strengths of the AHS, including the prospective study design and cumulative pesticide exposure assessment. Cases of incident RA were self-reported and while authors attempted to reduce over reporting using a screening tool among those reporting RA on the Phase 3 questionnaire to gather more information about the disease and medications prescribed for RA, these reports were not confirmed via medical record. As such, the outcome assessment was considered a limitation of the study. Additionally, the stepwise selection procedures were considered a limitation as these are generally appropriate only for studies conducting exploratory analyses for purposes of hypothesis generation; purported statistical significance arising from studies that use this technique are not valid and cannot be relied upon. However, since the study mentioned that "covariates were selected based on hypothesized or observed associations with rheumatoid arthritis" this infers that the stepwise procedure was not automated and instead relied on the thoughtful selection of covariates.

[45] Probable RA cases included those RA cases who reported disease-modifying antirheumatic drugs use (n = 220) and possible RA cases included those who reported use of steroids for RA or diagnosis or visit to rheumatologist (n = 160)

EPA Conclusion

Overall, there is *no epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and RA. There were two available publications (Parks et al., 2016, Meyer et al., 2017) that examined the association between dicamba exposure and RA among participants in the AHS prospective cohort and both reported no evidence of a positive association between dicamba exposure and RA. Parks et al. (2016) and Meyer et al. (2017) were ranked moderate quality and while benefited from exposure assessment approach used by the AHS, the outcome was self-reported and if clinically confirmed via medical records would have made the assessment stronger.

Birth Defects

Four studies (Arbuckle et al., 2001; Meyer et al., 2006; Weselak et al., 2008; Yang et al., 2014) examined the association between dicamba birth defects and spontaneous abortion.

- Arbuckle et al. (2001) evaluated the potential association between prenatal exposure to pesticides, including dicamba, and spontaneous abortions during pregnancy.[46] Using data from the Ontario Farm Family Health Study (OFFHS), a population based retrospective cohort study conducted in Canada, this study identified families residing on farms according to the 1986 Canadian Census of Agriculture. Eligible farm couples included those where the females were ≤ 44 years of age and both the male and female of the couple permanently resided on the farm throughout the prior year. Three questionnaires completed by the wife, the husband, and a farm pesticide applicator, if separate from the husband or wife, were used to assess self-reported reproductive history, including the main outcome spontaneous abortion of <20 weeks' gestation, and self-reported past pesticide exposures. Questionnaires completed by the wives focused on preconception and post-conception (during pregnancy)[47] pesticide exposures and requested a complete reproductive history including all previous pregnancies, including those that ended in spontaneous abortions. Estimated calendar month of conception, calculated by subtracting the gestational age at abortion or delivery from the delivery date, was mapped to a pooled history of agricultural and residential pesticide use gathered from the farm applicator (if different from husband or wife), husband, and wife to estimate exposure timing to either a pre- or post-conception time period. Logistic regression was conducted to calculate ORs and 95% CIs for individual pesticides without adjustment for any potential confounders. For both exposure periods (pre- and post-conception), the results were stratified as either an early spontaneous abortion (< 12 weeks) or a late spontaneous abortion (12-19 weeks). The husbands (or farm applicator, if someone other than the husband) reported pesticide exposures including the active ingredients contained within each pesticide. Among the total 3,936 pregnancies 395 spontaneous abortions were reported (226 early spontaneous abortions and 169 late spontaneous abortions). For the association between dicamba exposure during the preconception phase and spontaneous abortion, no evidence of a positive association was reported for all spontaneous abortions combined (Crude OR = 1.00; 95% CI: 0.70, 2.70; with n = 20 dicamba exposed cases). When preconception exposure to dicamba was stratified by early (<12 weeks gestation) and late (12-19 weeks gestation) spontaneous abortion, no evidence of a positive association was reported for early spontaneous abortions (Crude OR = 1.00; 95% CI: 0.50, 1.80; with n=11 dicamba exposed cases). No evidence of a significant positive association was reported for late spontaneous abortions (12-19 weeks gestation) (Crude OR = 1.10; 95% CI: 0.60, 2.20; with n=9 exposed cases). Similarly, for the association between dicamba exposure during the post-conception phase and spontaneous abortion, no evidence of a significant

[46] Spontaneous abortions were defined as an abortion that occurred prior to 20 weeks of gestation.
[47] Preconception was defined as a 4-month period spanning from three months prior to conception through the calendar month of conception. Post-conception was defined as a 3-month period spanning from the first calendar month after conception through the end of the first trimester.

positive association was reported for all spontaneous abortions combined (Crude OR – 1.10; 95% CI: 0.70, 1.90; with n = 15 exposed cases) and for late spontaneous abortions (12-19 weeks gestation) (Crude OR – 1.60; 95% CI: 0.80, 3.20; with n = 9 exposed cases) and no evidence of a positive association was reported for early spontaneous abortions (Crude OR – 0.80; 95% CI: 0.30, 1.70; with n = 6 exposed cases).

A further analysis that assessed the effects of pre-conception exposure vs. post-conception exposure on the association between dicamba and spontaneous abortions (all combined, early, and late) reported no evidence of a significant positive association for the early spontaneous abortions (Crude OR = 1.40; 95% CI: 0.40, 4.70; with n=9 pre- and n=4 post-conception exposed cases). No evidence of a positive association was reported for late spontaneous abortion (Crude OR = 0.60; 95% CI: 0.20, 1.60; with n = 7 pre- and n = 8 post-conception exposures to dicamba) and all spontaneous abortions (any gestational age) (Crude OR = 1.00; 95% CI: 0.40, 1.90; with n = 15 exposed cases). And finally, the risk of early vs. late spontaneous abortion was compared during each time period of exposure (preconception, post-conception). For both exposure time periods, preconception and post-conception exposure to dicamba, no evidence of a positive association was reported between dicamba exposure and early spontaneous abortions relative to late spontaneous abortions, with the late spontaneous abortion category as the referent (*Preconception exposure* – Crude OR = 0.90; 95% CI: 0.40, 2.20; with n = 11 early and 9 late spontaneous abortions; *Post-conception exposure* – Crude OR = 0.50; 95% CI: 0.20, 1.40; with n = 6 early and 9 late spontaneous abortions).

The study quality of Arbuckle et al. (2001) was considered moderate quality based on the Framework. Despite being a population-based cohort study, exposure and outcome information were both gathered retrospectively by self-report without any corroboration or confirmation (pesticide use data or medical record abstraction). Authors estimated pesticide exposure by month and estimated gestational age at time of spontaneous abortion and then merged the two to create an estimated pesticide exposure by gestational period (preconception, post-conception) to assess the association between pesticide exposure and spontaneous abortion. This method allowed for the possibility of exposure misclassification. Spontaneous abortion was self-reported and it is possible that wives misremembered certain details about the event. Additionally, since dosing information was not provided in this study, the degree of exposure for each study subject was unknown and could have potentially led to misclassification. Also, because several couples included within the study were reporting on several past pesticide exposures and past pregnancies, and assuming some pregnancies led to poor outcomes (i.e. abortions), recall bias could have occurred and ultimately affected the woman's behavior for future pregnancies and couples' memory of pesticide exposure. Lastly, a small number of exposed cases were observed.

- Weselak et al. (2008) evaluated the potential association between pesticide exposures, including dicamba, among expectant farm couples and birth defects in their offspring. Using data from the Ontario Farm Family Health Study (OFFHS), Weselak et al. (2008) analyzed farm couple's exposures during pregnancy, specifically during the pre-conception and post-conception periods and birth defects among their children.[48] Mothers self-reported birth defects diagnosed at birth or since birth via questionnaire. A maternal fetal medicine physician and other authors catalogued birth defects by ICD-9 codes and pregnancies ending in one or more birth defects or musculoskeletal defects were included in the analysis. Birth defects pertaining to cleft lip/palate, urogenital, heart, integument, musculoskeletal defects, face and neck, chromosomal, digestive, and central nervous system were

[48] Pre-conception was defined as a 4-month period and spanned from 3 months prior to conception through conception (calendar month of). Post-conception was defined as a 3-month period and spanned after conception (first calendar month of) through the end of the first trimester.

considered within this study. For the exposure assessment, data was pooled from questionnaires completed by the wife and the husband, in addition to a farm applicator if separate from the husband or wife. Exposure questionnaires captured exposure details regarding pesticide applications, with the addition of a direct chemical activities assessment. Logistic regression used to estimate individual ORs and 95% CIs for pesticides including dicamba, adjusting for known risk factors for birth defects including: maternal fever during pregnancy, maternal age at conception, parity, and child's gender. Covariates with ORs <0.8 or >1.20 were added individually to the model and if this changed the exposure OR by 10% or more, the covariate was included in the final model. Among the 3,347 pregnancies, 118 birth defects were reported. Of those with information regarding dicamba, 8 of 158 exposed and 100 of 3,254 unexposed to dicamba reported birth defects. No evidence of a significant positive association was reported for the association between parental dicamba exposure and birth defects in offspring, among a small number of cases (OR = 1.67; 95% CI: 0.79, 3.53; with n = 8 exposed cases). When stratified by gender, evidence of a moderately strong positive association was reported between preconception dicamba exposure and birth defects in male offspring, among a very small number of cases (OR = 2.42; 95% CI: 1.06, 5.53; with n = 7 exposed cases and n = 87 exposed noncases). Results for post-conception analysis of dicamba exposure and birth defects among male offspring were not reported.

The overall quality of the study was ranked moderate based on the study quality criteria in the Framework. Limitations included potential for recall bias where those couples that had a pregnancy resulting in a birth defect may remember exposures better than those who had a pregnancy resulting in healthy offspring. Since dosing information was not provided in this study, the degree of exposure for each study subject was unknown and could have potentially led to misclassification. Additionally, several couples included within the study reported on several past pesticide exposures and past pregnancies, and assuming some pregnancies led to poor outcomes (i.e. abortions), recall bias could have occurred and ultimately affected the woman's behavior for future pregnancies. Lastly, a small number of exposed cases were observed.

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- Meyer et al. (2006) conducted a population-based case-control study to evaluate potential associations between exposure to pesticides including dicamba and hypospadias (male birth defect in which the opening of the urethra is located on the underside of the penis instead of the tip), based on geographic proximity of maternal residence to agricultural pesticide applications in Arkansas. The study population included participants previously identified for a urogenital birth defects study. Cases were identified using the Arkansas Reproductive Health Monitoring System, a population-based birth defects registry that uses active surveillance of medical records and interviews to identify cases. Eligible cases included male children with hypospadias who were born between 1998 and 2002 and whose maternal residence was in eastern Arkansas and was a geocodable address at their time of birth. Controls were identified using birth certificates data obtained from the Arkansas Department of Health Vital Records Department and included the next two males born after each case who did not have a congenital malformation identified on the birth certificate and whose maternal residence recorded on the birth certificate was a geocodable address in the study area. Controls were frequency matched to cases on maternal race and all participants included in the analysis had information on potential confounders and gestational age that were obtained from birth certificates. Pesticide exposure was determined using a combination of land use information from Landsat satellite imagery (National Agricultural Statistics Service, 2004), annual pesticide application statewide summary data on the most commonly used pesticides obtained from agricultural databases (Agricultural Research Service, 2001), and timing of application data obtained from Arkansas Agricultural Statistics Service

(2005). ArcGIS (ESRI, Redlands, CA)[49] was used to determine pounds of each pesticide applied within a 500-m buffer around each residence during gestational weeks 6 – 16, the critical period of development of male external genitalia. Multivariable unconditional logistic regression was used to calculate ORs and 95% CIs for the association between maternal dicamba exposure and hypospadias, adjusting for paternal education level, maternal age, maternal race, weight gain during pregnancy, gestational age at birth, smoking (number of cigarettes smoked per day during pregnancy). Backwards elimination was used to identify additional covariates associated with hypospadias, including timing of first prenatal care visit, parity, and an exposure metric representing total pesticide use. Pounds of dicamba applied within a 500 m buffer of maternal residence at birth were analyzed as both continuous and as a categorical variable. Among the total participants in the analysis, 45 of 354 cases and 129 of the 727 controls were exposed to dicamba. In the analysis where dicamba exposure was treated as a continuous variable, no evidence of a positive association was reported for the association between maternal dicamba exposure based on residential proximity to dicamba use and hypospadias in their children (OR 1.00; 95% CI: 0.98, 1.02; with n=354 exposed cases). For the categorical analysis, pounds of pesticides applied were divided into four exposure categories using Jinks method in ArcGIS. The top two exposure categories were combined because of small cell sizes size, to create three categories: 0, > 0 - <0.04, and ≥0.04 lbs of dicamba applied per 500 m. No evidence of a positive association was reported between pounds of dicamba applied within 500 m of maternal residence at birth and hypospadias in children, with the no exposure group as the referent (*>0 - <0.04 lbs* – OR = 0.53; 95% CI: 0.30, 0.95; with n = 34 exposed cases, *≥0.04 lbs* – OR = 0.91; 95% CI: 0.38, 2.14; with n = 11 exposed cases).

The quality of the study was ranked moderate. Strengths included the case-control study design, case ascertainment using a medical birth defect registry, and objective measure of exposure thus removing potential for recall bias. The primary limitation of the study was that it relied on a geospatial approach to assess pesticide exposure based on residential address and land use data on dicamba. This approach helps minimize recall bias however, the method relied on a 500 m buffer to assign ever/never exposure based on distance to agricultural land where dicamba was reported to have been applied. This approach has not been validated so it is unclear if residence within 500 m of agriculture land can provide a reliable estimate of maternal exposure during pregnancy. Additionally, the study did not account for possible residential mobility[50] of mothers between pregnancy and childbirth with residency geocoded only for maternal address at delivery. As a result, the maternal residential addresses during the exposure period may have differed from the reported addresses at childbirth that were geocoded and used to determine exposure at 6 - 16 weeks gestation, possibly causing exposure misclassification. Additional limitations include potential for outcome misclassification due to reliance on birth certificates for data about control participants including covariates and birth defect status. Birth certificates may underreport birth defects and data quality varies between hospitals and states.[51]

Commented [JE17]: find reference for residential mobility of pegnant women

[49] ArcGIS (ESRI Redlands, CA) software was used to determine acres of crops cultivated within a 500-m buffer around each home. Dates containing exposure period for each subject were then linked with estimated dates of crop specific pesticide applications and field dissipation half-lives. Authors cross referenced pesticide use data for each application with acres grown for each crop type within the 500-m buffer and calculated an estimated use (pounds of active ingredient) for each pesticide during the exposure period for each subject.

[50] Research based on the Birth Defects Risk Factor Surveillance Study in Georgia found that 22% of women moved during pregnancy, with half moving outside of the county and that pregnant women were more likely to move if they were younger, did not plan their pregnancy, and smoked; SES, fathers age, and parity also affected the probability of moving. With respect to distance moved, the study found that of those who did move, about 60% did so for more than 8 miles (Miller et al., 2009).

[51] National Birth Defects Prevention Network (NBDPN). *Guidelines for Conducting Birth Defects Surveillance.* Sever, LE, ed. Atlanta, GA: National Birth Defects Prevention Network, Inc., June 2004.

- Yang et al. (2014) conducted a case-control study of the San Joaquin Valley of California to examine the association between pesticide exposure, including dicamba and neural tube defects and orofacial clefts. The study used the California Birth Defect Monitoring Program to identify all cases of birth defects from October 1997 to December 2006. Cases included and infants/fetuses clinically diagnosed with anencephaly, spina bifida (SB), or cleft lip with or without cleft palate (CLP) or cleft palate alone. Controls included nonmalformed live-born infants and were randomly selected from birth hospitals to represent the target population of the cases. After identifying potential cases and controls, the investigators conducted maternal interviews by telephone between 6 weeks and 24 months after the infant's estimated date of delivery. Among those eligible for the analysis, 71% of cases (n = 763) and 69% of controls (n = 974) completed the interviews and provided data on a range of covariates on education, nutrition, maternal address, lifestyle, and socioeconomic status. For each case/control, ever/never pesticide exposure was ascertained based on residential proximity to agricultural pesticide applications during early pregnancy, based on a 1,000 m buffer around maternal residential addresses. Pesticide exposure was measured for each case or control mother from 1 month before to 2 months after her reported date of conception. To estimate pesticide applications, the study obtained statewide pesticide use reporting records from January 1997 to December 2006, from the California Department of Pesticide Regulation Pesticide Use Reporting (PUR) data. Multivariable logistic regression was then used to assess the relationship between ever/never use of 461 pesticides, including dicamba, and neural tube defects and orofacial clefts. This analysis adjusted for race/ethnicity, educational level, pre-pregnancy BMI, parity, folic acid supplement intake, and smoking during 1 month before and the first 2 months of pregnancy. Analysis for clefts were further stratified by infants' sex. Based on this approach, the investigators reported no evidence of a significant positive association between dicamba exposure and odds of cleft palate alone (OR = 1.4, 95% CI 0.4, 5.1; n=5 dicamba exposed mothers). Results were not calculated for cleft lip with or without cleft palate, anencephaly and spina bifida due to no or too few exposed cases.

  Overall Yang et al. (2014) was considered moderate quality based on the OPP Framework. The primary strength of the study was that its population-based approach used the California Birth Defect Monitoring Program and birth registry to systematically identify birth defect cases and healthy births in the San Joaquin Valley, California. The investigators were also able to collect detailed information on a range of potential confounders that included education, nutrition, maternal address, lifestyle, and socioeconomic status. The primary limitation of the study was that it relied on a geospatial approach to assess pesticide exposure based on residential address and California PUR data on dicamba. This approach helps minimize recall bias but relied on a 1,000 m buffer to assign ever/never exposure based on distance to agricultural land where dicamba was reported to have been applied. This approach has not been validated so it is unclear if being present within 1,000 m of agriculture land can provide a reliable estimate of maternal exposure during pregnancy. Finally, we note that there were a limited number of exposed based on this approach, including 5 dicamba-exposed cases.

Commented [AN18]: For David – note that we have discussed whether these GIS case-control studies should be rated moderate or low. I have ranked moderate to be consistent with our previous review of a similar study by Carmichael et al, but have noted the limitations of the exposure assessment.

Commented [DM19R18]: Ok. Let's discuss.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and birth defects that included neural tube defects, hypospadias, orofacial clefts, and spontaneous abortion. Four publications (Arbuckle et al., 2001; Meyer et al., 2006; Weselak et al., 2008; Yang et al., 2014) examined the association between dicamba exposure and birth defects. Two publications (Arbuckle et al., 2001; Weselak et al., 2008) utilized the Ontario Farm Family Health Study (OFFHS), a population-based retrospective cohort study conducted in Canada, to evaluate the effect of dicamba on birth defects. Arbuckle et al. (2001) reported no evidence of a significant positive association between dicamba exposure and spontaneous abortion. Weselak et al. (2008) reported no evidence of a significant positive association for the association between parental

dicamba exposure and birth defects in offspring, among a small number of cases and when stratified by gender, reported evidence of a moderately strong positive association between preconception dicamba exposure and birth defects in male offspring among a very small number of exposed cases. We note the very small number of dicamba exposed cases which severely restricts the ability to interpret with confidence the observed odds ratios. We also note that there were too few cases to assess the post-conception defects among male offspring and too few female cases with dicamba exposure to asses any association with birth defects. Both studies were ranked moderate quality and both had limitations including the potential for recall bias, exposure misclassification, outcome misclassification. Meyer et al. (2006), conducted a population-based case-control study using a birth defects registry to identify cases and geospatial information about pesticide use and maternal residence during gestational weeks 6–16 to evaluate prenatal dicamba exposure and hypospadias in male offspring in Arkansas. Authors reported no evidence of a positive association. Using a similar method, Yang et al. (2014) used California registry data on birth defects and healthy births to identify cases and controls and CA PUR to ascertain exposure to dicamba and reported no evidence of a significant positive association between dicamba exposure based on maternal residence at birth and cleft palate in offspring. As such, both studies had similar strengths, but had substantive limitations in their exposure assessment because it is unclear if living within a certain distance (500m or 1,000 m) of agriculture land is a reliable indicator of maternal exposure to dicamba. Furthermore, we note the very small number of exposed cleft palate cases which severely restricts the ability to interpret with confidence the observed odds ratios.

Birthweight

One study (Sathyanarayana et al., 2010), examined the association between maternal dicamba exposure and birthweight in their children.

Sathyanarayana et al. (2010) investigated in a cross-sectional study the potential association between maternal exposure to pesticides including dicamba and subsequent birthweight among participants of the AHS. The study population consisted of female spouses enrolled in the AHS who had given singleton[52] birth within 5 years of study enrollment and had complete information on all covariates (n = 2,246). Self-administered questionnaires were used to assess pesticide exposure and to obtain detailed information regarding pregnancy. Using this response data, overall pesticide exposure was first categorized based on pesticide-related tasks as one of the following: no exposure, indirect exposure, residential exposure, or agricultural exposure[53] during the first trimester of pregnancy for each study participant. Individual pesticide exposures were then assessed based on ever/never use. The outcome was defined as birth weight, a continuous variable, in grams. A linear regression model was used to estimate change in birth weight[54] for overall pesticide exposures based on the categorized exposures, in addition to 27 individual pesticides, adjusting for maternal BMI (considered both as BMI and BMI squared), height, parity, smoking, and state of residence as well as preterm status. Of the 2,246 females who reported live birth pregnancies, 1,162 (52%) indicated no exposure to pesticides, and 764 (34%), 278 (12%), and 42 (2%) reported indirect, residential, and agricultural exposures during their first trimester of pregnancy, respectively. No evidence of a significant association was determined in birthweight at each of the four categories of exposure (-72 grams $\leq \beta \leq$ 9 grams; all CIs encompassed the null value of 0; n = 42 – 764 women). No evidence of a significant reduction was reported between mother's ever use of dicamba and offspring's birth weight (β = -24 grams; 95% CI: -162, 114 grams; with n = 50 exposed participants).

[52] Singleton birth defined as a birth event that resulted in a single, live born child.
[53] No exposure = women who answered negatively to all exposure questions; indirect exposure = pruning, picking, harvesting, or weeding; residential exposure = applying pesticides within the home or garden; agricultural exposure = applying or mixing pesticides to crops or fixing pesticide application equipment.
[54] Change in birth weight reported as a multiple regression estimate coefficient with an associated 95% CI in grams.

The quality of the study was ranked low based on the study quality criteria provided in the OPP Framework. The cross-sectional study design was the main limitation since temporality for exposure in relation to the outcome could not be determined, thus the study was ranked low quality.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between maternal dicamba exposure and birthweight in children. One publication, Sathyanarayana et al. (2010), examined the association between maternal dicamba exposure and birthweight in their children among the AHS population and reported no evidence of a significant association between mother's ever use of dicamba and offspring's reduced birth weight. The study quality was ranked low due to the cross-sectional study design since temporality for exposure in relation to the outcome could not be determined.

Depression

Two studies (Beard et al., 2013; Beard et al., 2014) examined the association between dicamba exposure and depression.

- Beard et al. (2013) investigated the potential association between pesticide exposure, including dicamba, and incident depression among wives of farmers enrolled in the AHS prospective cohort. The study population consisted of female spouses (n = 16,893) enrolled in the AHS, living in Iowa and North Carolina, with no history of physician diagnosed depression at enrollment, had complete data on depression at enrollment, and had complete covariate data. Cases included farmers' wives who self-reported incident depression between the time of study enrollment (1993-1997) through study follow-up (2005-2010), and cases were ascertained through responses to questions during the telephone follow-up interview. The noncases included farmer's wives who did not report incident depression. Exposure was assessed during study enrollment for 50 different pesticides including dicamba using self-administered questionnaires. Of the 1,054 cases, 31 (3%) reported exposure to dicamba. The association between dicamba ever use, and indirect exposure through farmer's use of dicamba and incident depression among farmers' wives was estimated using log-binomial regression to determine RRs and 95% CIs. Inverse probability weights were applied to adjust for education level, age at enrollment, ever diagnoses with diabetes, state of residence, and drop out, as well as to account for the substantial number of women (n = 10,639) within the study population who did not complete a follow-up interview (1,342 due to death). No evidence of a positive association was reported for wives' dicamba ever use and self-reported incident depression (RR = 0.75; 95% CI: 0.52, 1.08; with n = 31 exposed cases,) and no evidence of a positive association was reported for husband's ever use of dicamba and self-reported incident depression among wives' who never used dicamba (RR = 0.96; 95% CI: 0.77, 1.20; with 208 (52%) cases with indirect exposure).

  The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The ranking was based on the general strengths of the AHS, including its prospective design and exposure assessment approach which examined lifetime exposure to dicamba. However, the outcome was self-reported without medical record validation and pesticide exposure was self-reported, which may have introduced exposure misclassification and was limited to ever use. Information on frequency and duration of use of pesticides was not available for wives.

- Beard et al. (2014) investigated potential association between pesticide exposure, including dicamba, and self-reported depression among male pesticide applicators in the AHS prospective cohort. The

study population included male pesticide applicators, enrolled in the AHS between 1993 – 1997, who also completed a follow up telephone interview between 2005 – 2010. Participants self-reported physician diagnoses of depression prior to enrollment only, at both enrollment and follow-up, or at follow-up only. Pesticide exposure was assessed via two self-administered questionnaires, completed during study enrollment and during the follow-up interview (2005-2010). Polytomous logistic regression was used to calculate ORs and 95% CIs for dicamba. Inverse probability weighting adjusted for confounders including age, diabetes, education level, and state of residence, and accounted for subjects missing covariate data and study drop-outs. Among the study population (n = 21,208), 1,702 (8%) reported receiving a diagnosis of depression (cases). Of those 1,702 cases, 474 reported a diagnosis of depression at enrollment but not follow-up, and 248 (54%) of those cases reported exposure to dicamba. Of the 1,702 cases, 540 participants reported depression diagnosis at both enrollment and follow-up, and 292 (57%) of those cases reported exposure to dicamba. Of the 1,702 cases, 688 participants reported depression diagnosis at follow-up only, and 365 (57%) of those cases reported exposure to dicamba. There were 19,506 study participants who reported no physician diagnosis of depression, and 10,237 of those non-cases reported exposure to dicamba. No evidence of a positive association was reported between dicamba exposure and risk of depression for those who reported depression at enrollment only (OR = 0.90; 95% CI: 0.70, 1.10) or for those who reported depression at follow-up only (OR = 1.00; 95% CI: 0.80, 1.20). And there was no evidence of a positive association reported between dicamba exposure and risk of depression for those who reported depression at both enrollment and follow-up (OR = 1.00; 95% CI: 0.80, 1.20).

The study quality was ranked moderate based on the study quality criteria provided in the OPP Framework. The ranking was based on the general strengths of the AHS, including its prospective design and exposure assessment approach which examined lifetime exposure to dicamba. The study relied on the self-report of depression diagnosis. Confirmation of cases via medical records would have improved the reliability of the outcome classification of the study.

EPA Conclusion

Overall, there is *no epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and depression. There were two available studies (Beard et al., 2013; Beard et al., 2014) of the AHS cohort that examined the association between dicamba exposure and depression among male pesticide applicators and among wives of farmers. Beard et al. (2013) reported no evidence of a positive association for wives' dicamba ever use and self-reported incident depression, and no evidence of a positive association based on husband's ever use of dicamba as an exposure proxy. Similarly, Beard et al. (2014), reported no evidence of a positive association was between dicamba exposure and depression amongst those who reported depression at enrollment only, at follow-up only, and at both enrollment and follow-up. Both studies were rated moderate quality and relied on self-reported physician diagnosis of depression rather than clinical or medical record confirmation.

Diabetes

Two studies (Montgomery et al., 2008; Starling et al., 2014) examined the association between dicamba exposure and diabetes.

- Montgomery et al. (2008) investigated the association between pesticide exposure, including dicamba, and incident diabetes among pesticide applicators in the AHS prospective cohort. The study population consisted of pesticide applicators enrolled in the AHS between 1993 and 1997 (n = 33,457), living in Iowa or North Carolina, who completed both the enrollment (1993-1997) and

follow-up (1999-2003) questionnaires and did not report diabetes at enrollment. Incident diabetes was identified via self-report at the 5-year follow-up interview. Pesticide exposure was assessed using self-reported data from the enrollment and follow-up questionnaires. Among the 1,176 diabetic cases, 434 (43%) reported ever use of dicamba, and among the 30,611 non-cases with complete data, 14,639 (53%) reported ever use of dicamba. The association between dicamba exposure and diabetes was assessed using logistic regression to estimate ORs and 95% CIs, adjusted for age, state of residence, and body mass index (BMI). No evidence of a positive association was reported between dicamba and diabetes (OR = 0.68; 95% CI: 0.60, 0.78; with n = 434 exposed cases and n = 14,639 exposed non-cases) based on ever use when adjusted for age only. Further adjusting the model for state of residence and BMI in addition to age, no evidence of a positive association was reported (OR = 0.99; 95% CI: 0.85, 1.15; with n = 434 exposed cases and n = 14,639 exposed non-cases).

The study quality was ranked moderate based on the study quality criteria provided in the OPP Framework. The prospective cohort study design as part of the AHS and the detailed pesticide exposure assessment were strengths. Self-reported diagnosis of diabetes among the study participants and the inability to control for diet and exercise were considered study limitations and may have resulted in misclassification of some of the observed results and/or errors induced by confounding, respectively. The potential for selection bias was also present since a large number of participants who did not complete a follow-up questionnaire might have been diabetic at study enrollment. The study authors reported that "although we had relatively good follow-up of the cohort after 5 years, participants who did not complete the follow-up interview were more likely to have had diabetes at enrollment."

- Starling et al. (2014) investigated the potential association between pesticide exposure, including dicamba and diabetes among wives of farmers in the AHS study. The study population included female spouses (n = 13,637) of farmers who were part of the AHS, living in Iowa and North Carolina who reported ever mixing or applying pesticides prior to enrollment, completed at least one of the two follow-up interviews at 5-years or 10-years after enrollment (N = 15,034), self-reported a physician-diagnosis of diabetes after enrollment and who had complete information on BMI. Pesticide exposure was assessed using data gathered on enrollment questionnaires. Cox proportional hazard regression models were used to calculate HRs and 95% CIs to analyze the association between ever use of dicamba and incident diabetes among wives of farmers in the AHS, adjusting for BMI at enrollment and state of residence. Of the total 688 cases, 54 (8%) reported exposure to dicamba, and of the 12,949 non cases, 916 (7%) reported dicamba exposure. No evidence of a significant positive association was reported between dicamba ever use and incident diabetes in women (HR = 1.15; 95% CI: 0.86, 1.53).

  The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Self-reported diagnosis of diabetes among the study participants and the inability to control for diet and exercise were considered study limitations and may have resulted in misclassification of some of the observed results and/or errors induced by confounding, respectively.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and diabetes. Montgomery et al. (2008) reported no evidence of a positive association between ever use of dicamba and diabetes among pesticide applicators. Starling et al. (2014) reported no evidence of a significant positive association between dicamba use and incident diabetes in women based on ever use. Self-reported diagnosis of diabetes among the study participants and the inability to control for diet and exercise were considered study

limitations in both studies and may have resulted in misclassification of some of the observed results and/or errors induced by confounding, respectively. Additionally, in Montgomery et al. (2008), the potential for selection bias was also present since a large number of participants who did not complete a follow-up questionnaire might have been diabetic at study enrollment.

Dream Enacting Behaviors

One epidemiologic study (Shrestha et al., 2018a) was identified that assessed exposure to dicamba and dream enacting behaviors (DEB) among farmers enrolled in the AHS.

Shrestha et al. (2018a) examined the association between pesticide exposure, including dicamba, and DEB using data from the AHS cohort. The study population included male private pesticide applicators in the AHS, living in Iowa and North Carolina, who completed a follow-up interview (2013 – 2015) that screened for several Parkinson's disease prodromal symptoms including DEB. AHS participants self-reported information on DEB in response to , "Have you ever been told, or suspected yourself, that you seem to 'act out dreams' while sleeping?" If they answered yes, they were prompted to answer additional questions on the frequency of symptoms. Participants self-reported physician-diagnosed Parkinson's disease during follow-up interviews and cases of DEB were validated using medical record data. Information on head injury was obtained from a subsequent take-home questionnaire and the Phase II follow-up questionnaire in 1999-2003. Pesticide exposure was reported through self-administered questionnaires completed at enrollment (1993 – 1997). Multivariable logistic regression was used to assess the relationship between pesticide exposure and DEB, adjusting for age, smoking, alcohol consumption, marital status, education, state of residence, and head injury. Authors used inverse probability weighting to impute missing data to account for the loss of participants and loss of covariates as only 23,478 (46%) of the 51,035 male private applicators in AHS completed the follow-up survey (2013-2015). Among the 20,591 male private applicators included in the analysis, 1,623 (7.9%) self-reported DEB during the follow-up interview and 1,001 of these also reported experiencing DEB symptoms three or more times. Among the 1,623 cases, 780 DEB cases reported exposure to dicamba. Cases were compared with cohort members who also completed the follow-up interview but did not report DEB (n = 16,441). No evidence of a positive association was reported between dicamba ever use and DEB among male pesticide applicators (OR = 1.00; 95% CI: 0.90, 1.20; with n = 780 exposed cases). Similarly, no evidence of a positive association was reported between dicamba exposure and DEB among pesticide applicators who reported three or more episodes of DEB (N = 17, 321), (OR = 1.00; 95% CI: 0.90, 1.20, with n = 495 exposed cases). And finally, no evidence of a positive association was reported between dicamba ever use and DEB when PD patients were excluded (OR = 1.00; 95% CI: 0.90, 1.20, with n = 740 exposed cases).

The overall study quality was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths included the cohort study design and the reliability of the AHS questionnaire to ascertain pesticide exposure. While the study had several strengths, it was determined to be of moderate quality because of limitations in the ascertainment of the outcome and the potential risk of selection bias due to loss to follow-up. Ascertainment of the outcome relied on self-report by survey participants and may have introduced misclassification if participants cannot reliably report that their symptoms are consistent with typical prodromal PD symptoms. Given that the study was prospective, this source of outcome misclassification is likely to be non-differential because study subjects provided information on pesticide use before reporting DEB during Phase 5 follow-up in 2013-2015. Loss to follow-up is another important limitation because only 46% of the study subjects originally enrolled completed the Phase 4 survey in 2013-2015. This may introduce selection bias if study subject participation in the follow-up phases is related to their disease status for PD and other health outcomes.

EPA Conclusion

Overall, there is *no epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba and DEB among farmers enrolled in the AHS. One available study (Shrestha et al., 2018a) assessed the association between dicamba and DEB among farmers in the AHS and reported no evidence of a positive association. The overall quality of the study was ranked moderate. Study limitations included the self-reported outcome and the potential risk of selection bias if study subject participation in the follow-up phases was related to their disease status for PD and other health outcomes.

End Stage Renal Disease

Two studies (Lebov et al., 2015; Lebov et al., 2016) examined the association between dicamba exposure and end stage renal disease (ESRD).

- Lebov et al. (2015) evaluated the association between pesticide exposure, including dicamba and ESRD. The study population consisted of female spouses of pesticide applicators enrolled in the AHS. ESRD cases were identified through linkage with the US Renal Data System and first renal replacement therapy (i.e. dialysis initiation or renal transplantation) date was used to identify ESRD cases occurring between study enrollment (1993-1997) and end of follow-up (December 31, 2011). Pesticide exposure was assessed using information obtained via self-administered questionnaires completed at enrollment, however, results for direct exposure to dicamba (wives personal use) were not reported. The number of cases and non-cases with direct dicamba exposure was not reported. Among the 64 ESRD cases and the 13,653 non-cases with indirect exposure to pesticides who reported no prior use, 28 (54.9%) cases and 6,072 (49.4%) non-cases reported indirect exposure to dicamba. No evidence of a significant positive association was reported for indirect exposure to dicamba and ESRD among female spouse of pesticide applicators who had no prior use of dicamba themselves (HR = 1.39; 95% CI: 0.80, 2.42; with n = 28 exposed cases). In an additional analysis that considered the association between husbands' cumulative lifetime use of dicamba and ESRD among wives who reported no direct pesticide exposure, husband's dicamba lifetime exposure was divided at the following cut points at the median: 1.0 – 25.3 days of use and > 25.3-262.9 days of use. No evidence of a significant positive association was reported for female spouses' indirect dicamba exposure at either exposure level and no evidence of an exposure-response trend (*1.0 – 25.3 days of use* – HR = 1.30; 95% CI: 0.66, 2.57; with n = 13 exposed cases; *>25.3-262.9 days of use* – HR = 1.42; 95% CI: 0.70, 2.86; with n = 123 exposed cases; p-trend > 0.05), with the non-exposed group as the referent.

  The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The general strengths of the study were the underlying prospective design of AHS, focus on U.S. agricultural populations, and availability of a U.S. registry to comprehensively identify ESRD cases. Study limitations included the indirect assessment of pesticide exposure for applicator wives using husband use information as a surrogate. This approach has not been validated and may not be a reliable proxy for direct exposure by female spouses.

- Lebov et al. (2016) evaluated the association between pesticide exposure, including dicamba, and ESRD among male pesticide applicators enrolled in the AHS prospective cohort. The study population included male pesticide applicators, enrolled in the AHS (1993 – 1997), living in Iowa and North Carolina, who were >18 years old. ESRD cases were identified from enrollment through follow-up (December 31, 2011) by linking the AHS cohort data with the United States Renal Data

System. Pesticide exposure was assessed via self-administered questionnaires administered at enrollment and shortly thereafter at home. For several pesticides, including dicamba, only duration and frequency information were available on the take-home questionnaire. Among the 24,429 with this limited exposure information, 136 ESRD cases were identified and of these, 95 cases reported dicamba exposure. Lifetime pesticide exposure was modified by an intensity factor to account for the variation in pesticide application practices to produce an estimate of IWLD of exposure for 39 pesticides including dicamba. An investigation of the association between IWLD of use of dicamba and ESRD among applicators, was conducted with the following tertiles: <490 days of use, 490 – 2,766.75 days of use, and ≥ 2,766.75 days of use, with the no exposure group as the referent. Cox proportional hazards models were used to calculate HRs and 95% CIs for the association between dicamba and ESRD among male pesticide applicators, adjusting for state and age. No evidence of a significant positive association was reported between dicamba exposure and ESRD among male pesticide applicators at any exposure category and no evidence of a significant exposure-response trend, with the no exposure group as the referent ($0.69 < HR < 1.06$; all 95%CIs encompassed the null value of 1.0; n = 31 - 32 exposed cases and n = 7,153 – 10,203 exposed non-cases; p-trend > 0.05).

The overall quality of the study was ranked high based on the study quality criteria provided in the OPP Framework. The general strengths of the study were the underlying prospective design of AHS, focus on U.S. agricultural populations, and availability of a U.S. registry to comprehensively identify ESRD cases. Lebov et al. (2016) directly assessed dicamba exposure based on the AHS survey instrument.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and ESRD. Two studies investigated the association between dicamba and ESRD among the AHS study population. Lebov et al. (2015) reported no evidence of a significant positive association between indirect dicamba exposure (through husband's exposure) and end-stage renal disease (ESRD) among the female wives of pesticide applicators enrolled in the AHS. The overall quality of the study was ranked moderate with the primary limitation being the indirect assessment of pesticide exposure for applicator wives using husband use information as a surrogate. This approach has not been validated and may not be a reliable proxy for direct pesticide exposure. Lebov et al. (2016) reported no evidence of a significant positive association between dicamba exposure and ESRD among male pesticide applicators, based on intensity-weighted lifetime days of exposure, with the no exposure group as the referent. The overall quality of the study was ranked high.

Eye Disorders

Two studies (Kirrane et al., 2005; Montgomery et al., 2017) assessed the association between dicamba exposure and eye disorders among wives of pesticide applicators.

- Kirrane et al. (2005) investigated the association between pesticide exposures, including dicamba and retinal degeneration and other eye disorders among wives of AHS pesticide applicators using a cross-sectional analysis of the AHS prospective cohort. The study population included wives of pesticide applicators living on a farm in Iowa and North Carolina who completed the spouse's questionnaire. Doctors diagnosis of retinal degeneration was self-reported on the spouse's questionnaire as was pesticide exposure. A total of 31,173 women self-reported both exposure (wives ever use of pesticides) and outcome (eye disorders) on questionnaires completed at enrollment (1993 – 1997). Logistic and hierarchical logistic regression modeling were used to evaluate potential associations

between dicamba exposure and eye disorders, adjusting for age and state of residence. The authors reported 4.80% (~ 13 – 14) of the 281 cases of eye disorders and 4.10%[55] of non-cases were exposed to dicamba. No evidence of a positive association was reported between dicamba exposure and eye disorders among a small number of cases, based on ever use (OR = 1.00; 95% CI: 0.40, 2.50).

The overall quality of the study was ranked low based on the study quality criteria provided in the OPP Framework. The ranking was based on the general strengths of the AHS, ability to identify cancer cases through linkage to cancer registries, and the exposure assessment approach which examined cumulative lifetime exposure to dicamba. However, because of the cross-sectional study design, it was impossible to determine temporality and the study was thus ranked low quality for this reason.

- Montgomery et al. (2017) conducted a nested case-control study among the AHS study population as a follow-up study to Kirrane et al., (2005) to determine if incident cases of age-related macular degeneration (AMD) were associated with previous pesticide exposure including dicamba. The study population included pesticide applicators and their spouses, enrolled in the AHS prospective cohort, who completed both enrollment (1993 - 1997) and follow-up telephone interviews (1999 - 2003 and 2005 – 2010) and were ≥ 50 years old on September 1, 2007 (AMD is rare before that age). Cases included AHS study participants (men and women) who self-reported either a physician diagnosis of AMD during 1994 to 2007 or early signs of AMD. AMD diagnosis was confirmed by review of medical records and supporting pathology or retinal photographs were reviewed by the study optometrist and ophthalmologist, respectively. Controls were selected from the cohort participants who did not have confirmed or possible AMD. Lifetime days of pesticide exposure was assessed via self-report on questionnaires administered at enrollment. The association between dicamba exposure and AMD was assessed using logistic regression to determine ORs and 95% CIs, adjusted for age, gender, and smoking. Among the total 161 cases and 39,108 controls, 44 (30%) cases and 12,012 (33%) controls reported exposure to dicamba. No evidence of a significant positive association was reported between dicamba and AMD based on ever/never exposure (OR: 1.10 95% CI: 0.70, 1.70; with n = 44 exposed cases and n = 12,012 exposed controls). When the data were further stratified by gender, no evidence of a significant positive association was reported between dicamba exposure and AMD among men based on ever/never exposure (OR: 1.20; 95% CI: 0.80, 1.90, with n = 42 exposed male cases and n = 11,201 exposed male controls). There were not enough females reporting dicamba exposure to assess the association between dicamba exposure and AMD among females. When incident AMD cases were stratified by early and late AMD and adjusted for age, gender and smoking status, no evidence of a significant positive association was reported for dicamba exposure and either early or late AMD when compared to controls among a small number of cases (Early AMD – OR: 1.20; 95% CI: 0.60, 2.40, with n = 18 exposed cases and n = 12,012 exposed controls; Late AMD – OR: 0.90; 95% CI: 0.50, 1.70, with n = 18 exposed cases and n = 12,012 exposed controls). And, when late AMD was compared to early AMD (reference group), no evidence of a positive association was reported (OR: 0.80; 95% CI: 0.3, 1.9, with n = 18 exposed late AMD cases and n = 18 exposed early AMD cases).

  In an additional analysis of the cumulative days of dicamba exposure where exposure was divided into three exposure categories, >0 - 10 days, >10 – 100, and >100 days of cumulative exposure, with the no exposure category as the referent, evidence of a significant positive association was reported for the high exposure category (OR = 1.90; 95% CI: 1.03, 3.50; with n = 15 exposed cases, n = 2,887 exposed controls; p-trend 0.112), with the no exposure group as the referent. No evidence of a

[55] The total number of noncases was not reported by the study authors (only various ranges) due to missing data. Thus, we are unable to calculate an exact number of noncases exposed to dicamba.

significant positive association was reported for any other exposure category (1.00 > OR > 1.10; all 95% CIs encompassed the null value of 1.0; with n = 10 – 16 cases per exposure category).

The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The ranking was based on the general strengths of the AHS, including its prospective design, ability to confirm AMD cases through review of medical records and retinal photographs, and exposure assessment approach which examined cumulative lifetime exposure to dicamba. Additionally, we note that the number of exposed cases was small in the exposure-response analysis ($n \leq 15$).

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba and eye disorders including AMD. There were two available studies that examined eye disorders (Kirrane et al., 2005; Montgomery et al., 2017). Kirrane et al. (2005), reported no evidence of a significant positive association between dicamba exposure and retinal degeneration among wives of farmers in a cross-sectional analysis of the AHS population and was ranked low quality. In an update to Kirrane et al. (2005) that included longer follow-up time and analysis of both pesticide applicators and pesticide applicators wives together and then separately, Montgomery et al. (2017) reported evidence of a positive association between dicamba and AMD in the highest exposure category in the exposure-response analysis but no evidence of an exposure-response trend and no evidence of a significant positive association was reported in any other exposure category. The study quality was ranked moderate. Lastly, we note that even though the overall study populations were large in both studies – Kirrane et al., 2005; Montgomery et al., 2017 – only a small number of cases ($n \leq 18$ cases) with exposure to dicamba were available for the exposure-response analysis between dicamba and eye disorders which limits the interpretability of the observed odds ratios.

Fatal Injury

One study (Waggoner et al., 2013) examined the association between dicamba exposure and fatal injury.

Waggoner et al. (2013) investigated the association between specific pesticides, including dicamba, and fatal injury among male private pesticide applicators enrolled in the AHS prospective cohort. The study population consisted of AHS male private pesticide applicators (n = 51,035) living in Iowa and North Carolina who completed both enrollment questionnaires (1993 – 1997). Fatalities were identified through state death registries and the National Death Index. Cases were defined as any mortality that occurred in an occupational setting, including motor vehicle accidents, from enrollment (1993 – 1997) until the end of follow-up (December 31, 2008) or date of death (whichever was earlier). The non-case group included private pesticide applicators who did not suffer from a deadly injury during the study, regardless of vital status. Pesticide exposure was self-reported on the enrollment questionnaires. Cox proportional hazards models were used to calculate HRs and 95% CIs for fatal injuries and individual pesticides based on ever/never exposure, adjusted for age and state. Among the total study population (n = 51,035), 22,952 (50%) private pesticide applicators reported exposure to dicamba. And of the 281 fatal injuries, 148 (49%) reported exposure to dicamba. No evidence of a significant positive association was reported between dicamba exposure and fatal injury among male private pesticide applicators in the AHS, based on ever/never use (HR: 1.02; 95% CI: 0.81, 1.28; with n = 148 exposed cases). In an exposure-response analysis, where the following four exposure categories were created based on frequency of use (days/year), 0, ≤ 2.5, > 2.5 -7, >7 days per year of use, no evidence of a significant positive association was reported for any exposure category (0.85 < HR < 1.42; all 95%CIs encompassed the null value 1.0; with n = 11 – 52 cases per exposure category; p-trend = 0.27) and no exposure-response trend.

The quality of the study was ranked low based on the study quality criteria provided in the OPP framework. While Waggoner et al. (2013) leveraged the AHS's prospective design and mortality data available through the National Death Index, it has important methodological limitations. The original aim of AHS was to examine the association between chronic pesticide exposure and cancer outcomes. In contrast to cancer, fatal injury is an acute event so it is unclear if self-reported pesticide use at enrollment is a valid measure of exposure during the time interval that preceded fatal injury. The investigators also mention that frequency of pesticide use may be an "indicator" of other activities that could increase the risk of fatal injury. For example, individuals who use more pesticides may also use more complex farm equipment more frequently, increasing the chance of an occupational accident that could lead to death. As such, more definitive information is needed on cause of fatal injury and the contributing events that lead to accidents before any conclusions can be drawn from the AHS study population.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and fatal injury. There was one available study, Waggoner et al. (2013), that reported no evidence of a significant positive association between dicamba exposure and fatal injury among male pesticide applicators in the AHS. The study quality was ranked low. The prospective study design and collection of mortality data available through the National Death Index were study strengths, it is not clear if pesticide use at enrollment is a valid measure of exposure during the time interval that preceded fatal injury, as pesticide use could be more of an indicator of use of complex farm equipment which would increase risk of fatal injury.

Monoclonal Gammopathy of Undetermined Significance

The association between chlorothalonil exposure and monoclonal gammopathy of undetermined significance (MGUS), a pre-cursor to multiple myeloma, was evaluated in one AHS study (Landgren et al., 2009).

Landgren et al. (2009) investigated the potential association between pesticide exposure, including dicamba and MGUS among the AHS prospective cohort. MGUS is a pre-malignant disorder of the plasma cells that usually precedes multiple myeloma. The study population (n = 678) included a stratified random sample (based on lifetime of organophosphate use) of male pesticide applicators in the AHS cohort living in Iowa or North Carolina who completed all three follow-up phases of the AHS and were enrolled in a neurobehavioral study nested within the AHS cohort. Applicators who reported a history of lymphoproliferative malignancy were excluded. Cases of MGUS and non-cases were determined from participant serum samples collected between 2006 - 2007 for participants living in Iowa and in 2008 for participants living in North Carolina, as part of the neurobehavioral study. All study participants reported pesticide exposure through a self-administered questionnaire completed at enrollment (1993 – 1997) and occupational exposures, medical histories, and lifestyle factors at follow-up interviews conducted five years after enrollment. Logistic regression models were used to calculate ORs and 95% CIs for dicamba and risk of MGUS, adjusting for age and education level. Among the 678 male applicators included in the analysis, 17 of the 38 MGUS cases reported exposure to dicamba. No evidence of a positive association was reported between ever exposure to dicamba and MGUS among (OR = 0.90; 95% CI: 0.50, 1.80, with n = 17 exposed cases).

The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. The ranking was based on the general strengths of the AHS, including the prospective design, additionally the determination of MGUS cases through serum samples that were reviewed by

three study personnel. The exposure assessment approach only included ever/never use, and an exposure-response assessment of cumulative lifetime exposure to dicamba would have been helpful.

EPA Conclusion

Overall, there is *no epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba and dicamba. There available study (Landgren et al., 2009) reported no evidence of a positive association between dicamba exposure and MGUS among male pesticide applicators in a subset of the AHS population and was ranked moderate quality.

Myocardial Infarction

Two AHS studies (Mills et al., 2009; Dayton et al., 2010) examined the association between dicamba exposure and myocardial infarction (MI).

- Mills et al. (2009) evaluated the association between pesticide usage including dicamba, and MI among male pesticide applicators in the AHS prospective cohort. The study population (n = 54,609) included male pesticide applicators living in Iowa and North Carolina enrolled in the AHS. Cases of MI resulting in death among AHS participants that occurred after enrollment (1993 -1997) through December 31, 2006 were identified through linkage to state and national death records. Cases of incident non-fatal MI included those AHS participants who reported a physician diagnosis of MI since enrollment on the 5-year follow-up questionnaire (1999 – 2003). Fatal and non-fatal cases of MI were analyzed separately due to different follow-up times. Pesticide exposure was assessed using self-reported pesticide exposure on questionnaires completed at study enrollment and at the 5-year follow-up. Cox proportional hazards regression was used to calculate HRs and 95% CIs for fatal and non-fatal MI risk for individual pesticides, adjusted for age, smoking, and state of residence for the fatal MI analysis, and age, smoking, state of residence and BMI for the non-fatal MI analysis. Among the 476 fatal MI cases, 42% (n = ~ 223 - 224 reported exposure to dicamba, and of the 839 non-fatal MI cases, 47% (n = ~ 394 - 395) reported dicamba exposure. No evidence of a positive association was reported for self-reported ever use of dicamba and fatal MI (HR= 0.94; 95% CI: 0.75, 1.18; with n = ~ 223-224 exposed cases) and no evidence of a significant positive association was reported for dicamba exposure and non-fatal MI (HR= 1.13; 95% CI: 0.94, 1.34; with n = ~ 394 – 395 exposed cases).

  The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths include the prospective design of AHS and exposure assessment approach. With respect to limitations, fatal and nonfatal MI incidence were ascertained using state/national death registries and self-report, respectively. The use of registry data on mortality allowed the investigators to evaluate fatal MI in the entire AHS cohort, where non-fatal MI could only be evaluated in 32,024 of the total 54,609 participants enrolled in AHS (58%). The follow-up period for non-fatal MI was only a median time of 5 years, whereas the median follow-up time for fatal MI was 11.8 years. An additional limitation in the evaluation of non-fatal MI is that ascertainment relied on self-report and has not been validated. The investigators acknowledged limitation and suggest that this approach may result in misclassification, most likely non-differential, because studies in other populations suggest that only 60-68% of self-reported MI cases could be validated based on medical chart review.

- Dayton et al. (2010) conducted a prospective study of female participants of the AHS cohort to investigate the association between pesticide use, including dicamba, and non-fatal MI. A total of

22,425 women (pesticide applicators and spouses of pesticide applicators) who completed both the enrollment questionnaire and follow-up phone interview, self-reported physician-diagnosed MI and pesticide use including dicamba. Logistic regression was used to calculate ORs and 95% CIs, controlling for age, BMI, smoking status, and state of residence. Of the 168 incident MI cases, 5 (3%) reported exposure to dicamba; of the 22,257 controls, 1,019 (5%) reported exposure. Based on this approach, the investigators reported no evidence of a positive association between ever use of dicamba and non-fatal MI among farm women (OR=0.8, 95% CI 0.3-1.9, n=5 dicamba exposed cases).

The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths include the prospective design of AHS and exposure assessment approach. As with Mills et al. (2009), a limitation of the investigators' evaluation of non-fatal MI is that the outcome ascertainment relied on self-report and has not been validated. The investigators acknowledge this in the discussion of their findings and suggest that this approach may result in misclassification because studies in other populations suggest that only 60-68% of self-reported MI cases could be validated based on medical chart review.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba and MI. There were two studies of the AHS cohort that examined that association between dicamba exposure and MI. Mills et al. (2009) reported no evidence of a positive association for fatal MI and no evidence of a significant positive association for non-fatal MI, based on ever/never use of dicamba amongst male pesticide applicators in the AHS. Dayton et al. (2010) further examined the relationship between dicamba exposure and non-fatal MI among female participants of the AHS. The study reported no evidence of a positive association. Both studies were moderate quality and a limitation of both studies was the self-report of the outcome which could have resulted in misclassification.

Olfactory Impairment

One AHS study (Shrestha et al., 2020a) examined the association between dicamba exposure and olfactory impairment.

Shrestha et al. (2020a) evaluated the association between exposure to specific pesticides, including dicamba and olfactory impairment among pesticide applicators in the AHS. The study population consisted of private pesticide applicators (mainly farmers) enrolled in the AHS prospective cohort. Olfactory impairment[56] was self-reported during the Phase 4 follow-up interview (2013- 2016). Pesticide exposure was self-reported reported on the questionnaires administered at enrollment (Phase 1: 1993-2007) and shortly after and on follow-up interviews (Phase 2: 1999-2003, Phase 3: 2005-2010, and Phase 4: 2013-2016). Among the 52,394 applicators enrolled in the AHS, 24,145 completed the Phase 4 follow-up survey. Of these pesticide applicators who completed the Phase 4 follow-up questionnaire, 20,409 had complete data on olfaction and baseline covariates and were included in the final analysis. Logistic regression was used to estimate ORs and 95% CIs for the association between individual pesticides including dicamba use reported at enrollment and olfactory impairment among private pesticide applicators based on ever use and IWLD of use. Models were adjusted for age at enrollment, sex (male, female), smoking status, education, state of residence, and history of performing other farming tasks that

[56] Participants were asked to respond to two questions pertaining to olfactory impairment on the Phase 4 follow-up questionnaire and included "do you suffer from a loss of sense of smell or significantly decreased sense of smell?" and "When did you start losing your sense of smell" which had four possible response choices: ≤ 1, 1-5, and >10 years prior to the Phase 4 follow-up.

may result in airborne irritants at least once per year,[57] and correlated pesticides (ever use with Spearman correlation ≥ 0.40).[58] Among the 20,409 participants who reported olfactory impairment on the Phase 4 questionnaire, 1,158 cases of olfactory impairment and 9,506 (55.2%) noncases reported ever exposure to dicamba. No evidence of a significant positive association was reported between the association of dicamba ever use and olfactory impairment (OR = 1.11; 95% CI: 1.00, 1.24), based on ever use. In the exposure-response analysis, IWLD of dicamba (product of years of use and days per year weighted by exposure intensity) were divided into four exposure categories including never exposure (referent) and tertiles of days use for dicamba (>0–551, >551–2170, and >2170 days). No evidence of a significant positive association was reported for any exposure category of IWLD of dicamba use and olfactory impairment among pesticide applicators in the AHS ($1.09 \leq$ all ORs ≤ 1.15; all 95% CIs encompassed the null value of 1.0; with n = 366-396 cases per exposure category).

The quality of the study was ranked moderate quality based on the study quality criteria provided in the Framework. Study strengths included the AHS prospective cohort, and the exposure assessment including ever use and cumulative use exposure response analysis. The outcome was self-reported and the outcome assessment would have been strengthened by clinical confirmation of self-reported outcome.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and olfactory impairment. One publication (Shrestha et al., 2020a) examined the association between dicamba exposure and olfactory impairment among the AHS prospective cohort population and reported no evidence of a significant positive association between ever use and cumulative IWLD of use of dicamba among the pesticide applicators in the AHS and olfactory impairment. The quality of the study was moderate and even though benefited from the strengths of the AHS such as the prospective cohort study design and the exposure assessment. We noted limitations including the self-reported outcome assessment which could have been strengthened through clinical confirmation of olfactory impairment, the potential over adjustment of several covariates in the analysis. Additionally, authors adjusted for correlated pesticides however did not specify which pesticides were correlated with each other and this would have been helpful in the assessment.

Parkinson's disease

Two studies (Kamel et al., 2007; Shrestha et al., 2020b) assessed the association between dicamba exposure and Parkinson's disease (PD).

- Kamel et al. (2007) investigated the association between pesticide exposure, including dicamba, and PD in the AHS prospective cohort at enrollment and phase 1 follow-up. The study population (n = 52,393) consisted of male pesticide applicators and their spouses enrolled in the AHS living in Iowa and North Carolina who completed both the enrollment (1993 – 1997) and follow-up (1999-2003) questionnaires. Cases of PD included AHS study participants who self-reported a physician diagnosis of PD at enrollment (prevalent PD – n = 83 cases), and at the 5-year follow-up (incident PD – n = 78 cases) through 2003. Non-cases included AHS study participants who did not indicate PD at enrollment (n = 79,557) or at follow-up (n = 55,931). Pesticide exposure was assessed for 50 different pesticides including dicamba using self-administered questionnaires at study enrollment (1993 - 1997). Odds ratios and 95% CIs were calculated for the association between individual pesticides and

[57] Farming tasks that may result in airborne irritants (e.g., fumes, solvents, metals, and dusts) included repairing engines, handling stored grain, replacing asbestos brakes, welding, painting, and working in swine confinement areas.
[58] Correlated pesticides were not specified by authors.

PD using a hierarchical regression model, adjusted for state, age, and type of participant (applicator or spouse). Among the 78 incident cases of PD, 32 (47%) incident cases and 26 (35%) prevalent cases reported exposure to dicamba based on ever use. No evidence of a significant positive association was reported for dicamba exposure and incident PD (OR = 1.50; 95% CI: 0.80, 2.80; with n = 32 exposed cases) and no evidence of a positive association was reported for dicamba exposure and prevalent PD (OR = 0.90; 95% CI: 0.50, 1.60; with n = 26 exposed cases), based on ever use of dicamba.

The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Although study strengths included the AHS study cohort, several study limitations were noted, including the lack of clinical confirmation of self-reported PD cases and the potential for recall bias. Recall bias is particularly important because the study included prevalent PD cases that may recall previous exposures differently than study subjects without PD. Study authors also indicated that for the prevalent cases of PD, the diagnosis date was unknown in addition to the duration of use for pesticides, making it difficult to assess temporality (i.e. whether the disease preceded the outcome); this information was known for incident cases in this study.

- In a more recent study of the AHS cohort, Shrestha et al. (2020b) conducted a prospective study to further investigate the association between pesticide use, including dicamba, and incident PD among pesticide applicators and their spouses in the AHS. As with the previous study by Kamel et al. (2007), the study population for this analysis (n = 52,393) male pesticide applicators and their spouses living in Iowa and North Carolina, who completed the enrollment questionnaire (1993 – 1999) and at least one follow-up survey (Phase 2 -1999 – 2003, Phase 3- 2005 – 2010, Phase 4 - 2013 – 2016) or the PD validation screening questionnaire (2012 -2017). Cases of incident PD (n = 491) included AHS study participants who self-reported a physician diagnosis of PD on one of the follow-up questionnaires or on the PD validation survey, physical evaluation, medical records, or via linkage to state death registries and the National Death Index. The investigators then excluded prevalent cases of PD identified at enrollment and participants with inconsistent or insufficient information across follow-up surveys. Pesticide exposure was assessed using responses to the enrollment questionnaires and the Phase 2 questionnaire to determine ever use (applicators and spouses) and IWLD of use with exposure category cut-points at tertiles of IWLD among applicators. Cox proportional hazards regression was used to estimate HRs and 95% CIs for the potential association between pesticide exposure and PD, adjusting for sex, state of residence, education, smoking status, and ever use of correlated pesticides[59] (Spearman correlation $\geq$ 0.40). Among the 66,110 participants (applicators and spouses) included in the analysis, 17,945 (31%) non-cases and 161 (41.2%) cases reported dicamba exposure. No evidence of a positive association was reported for the association between ever use of dicamba and PD among pesticide applicators and spouses in the AHS (HR = 0.94; 95% CI: 0.72, 1.22; with n = 161 exposed cases). Similarly, the investigators reported no evidence of significant positive association between IWLD dicamba use and incident PD in any exposure category (based on the exposure categories >0 to $\leq$ 694, >694-$\leq$2,380, and >2,380) of IWLD of dicamba use (0.83 < HR < 1.25; all 95% CIs encompassed the null value 1.0; with n = 43 - 63 cases per exposure category; p-trend = 0.13).

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  Overall, Shrestha et al. (2020b) was of moderate quality based on the study quality criteria outlined in the OPP framework. The study expanded on the previous work of Kamel et al. (2007) and prospectively assessed the relationship between pesticide exposure, including dicamba, and incident cases of PD in the AHS cohort. Study strengths included the general design of the AHS, including its prospective design and ability to assess pesticide use in well-characterized agricultural study

[59] The authors did not specify correlated pesticides.

population in Iowa and North Carolina. The study was also able to follow-up on the AHS cohort through 2016 and identified 372 incident PD cases, whereas the previous study by Kamel et al. (2007) was limited to Phase 2 follow-up through 2005 and included only 72 incident PD cases. While the study had several strengths, the study also had several limitations related to Phase 3 and Phase 4 follow-up of the AHS cohort. Most importantly, selection bias may be present in the study because only 24,145 of the 52,394 applicators (46%) enrolled in the AHS cohort in 1993-1997 completed the Phase 4 follow-up survey. This degree of loss-to-follow could introduce selection bias and makes it difficult to assess the association between pesticide use and PD without additional information to evaluate the potential direction and magnitude of bias based on characteristics of study participants that were lost to follow-up. An additional limitation is that no additional information on pesticide use was collected during Phase 3 and Phase 4 of the AHS cohort. Follow-up during these phases covers a 13-year period of potential pesticide use, so this may have introduced exposure misclassification if subjects changed their pesticide use practices during that period. Finally, as with Kamel et al. (2007), the investigators ascertained incident PD cases based on self-report by study participants or through death records. This may introduce misclassification if there is disagreement between self-report of diagnosis and clinical exam by neurological specialists. The AHS investigators suggest that self-report of PD is reliable, based on previous work that showed 84% agreement between self-report of medical diagnosis and clinical confirmation (Tanner et al., 2011), but it is unclear how potential misclassification may impact the results reported by Shrestha et al. (2020b).

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and PD. There were two studies available, both evaluated agricultural study populations (Kamel et al., 2007; Shrestha et al., 2020b). Kamel et al. (2007) reported no evidence of a positive association between and was ranked moderate quality. Shrestha et al. (2020) was particularly notable because the study provides more recent, prospective follow-up of the AHS cohort through 2016 and included 372 incident PD cases. The study first examined ever-never use of dicamba at enrollment and incident PD in the entire AHS cohort and reported no evidence of a significant positive association between ever use of dicamba and incident PD and no evidence of a positive association and prevalent PD. Shrestha et al. (2020) further assessed cumulative, lifetime dicamba use among AHS applicators and reported no evidence of a significant positive association between dicamba use and incident PD in any exposure category of IWLD of dicamba use and no evidence of a significant exposure-response relationship.

Respiratory Effects

Eleven studies (Henneberger et al., 2014; Hoppin et al., 2002; Hoppin et al., 2006a; Hoppin et al., 2006b; Hoppin et al., 2007; Hoppin et al., 2008; Hoppin et al., 2009; Hoppin et al., 2017; Slager et al., 2010; Valcin et al., 2007; Weselak et al., 2007) examined the association between dicamba exposure and respiratory effects including asthma, chronic bronchitis, rhinitis, and wheeze.

Asthma

Four studies (Weselak et al., 2007; Hoppin et al., 2008; Hoppin et al., 2009; Henneberger et al., 2014) examined the association between dicamba exposure and asthma.

- Weselak et al. (2007) investigated the potential association between pesticide exposures including dicamba among farm couples and respiratory effects and allergies in their offspring. The study population was part of the Ontario Farm Family Health Study (OFFHS). Weselak et al. (2007)

analyzed farm couple's various exposures during pregnancy including pesticide exposure and respiratory effects (asthma bronchitis, persistent cough or bronchitis) and hay fever or allergies. Three questionnaires were mailed to participants, one for each the husband, wife, and the farm pesticide applicator if different form either the husband or wife. Wives were asked to report a full reproductive history of their first five pregnancies and their health outcome, as well as if a doctor had ever told them that their child had any of the following health conditions: asthma, chronic bronchitis or cough, and hayfever or allergies. For the exposure assessment, data on pesticide exposure from questionnaires completed by the wife and the husband, in addition to a farm applicator if separate from the husband or wife. Exposure questionnaires included questions about exposure details regarding pesticide applications, with the addition of a direct chemical activities assessment. Logistic regression was used to calculate ORs and corresponding 95% CIs for the association between dicamba exposure and the mentioned health conditions, adjusting for specific covariates within each analysis. Dicamba models were adjusted for child's age a time of questionnaire, father's age at conception, and income. Among the total number of offspring (n = 3,405) in this study, 2,243 offspring had parental exposure to any pesticide during gestation and 282 were exposed to dicamba. Among the 282 reported dicamba exposure during pregnancy, 10 reported asthma, 9 reported chronic bronchitis or cough, and 19 reported hayfever or allergies. For the analysis between dicamba exposure during pregnancy and asthma in offspring, no evidence of a positive association was reported for dicamba exposure during pregnancy and asthma among offspring (compared to pregnancies with no reported pesticide use during pregnancy) (OR = 0.70; 95%CI: 0.35, 1.40; with n =10 exposed cases). When adjusted for child's age at time of questionnaire, a covariate that when added to the crude model changed the exposure OR by 10% or more, no evidence of a positive association was reported (OR = 0.82; 95% CI: 0.39, 1.71; with n = 10 exposed cases).

Overall Weselak et al. (2007) was considered moderate quality based on the Framework. Despite being a population-based cohort study, exposure and outcome information were both gathered retrospectively by self-report without any corroboration pesticide use data or confirmation of outcome by medical record abstraction. Since dosing information was not provided in this study, the degree of exposure for each study subject was unknown and could have potentially led to misclassification. Also, because several couples included within the study were reporting on several past pesticide exposures and past pregnancies, and assuming some pregnancies led to poor outcomes (i.e. abortions), recall bias could have occurred and ultimately affected the woman's behavior for future pregnancies and couples' memory of pesticide exposure. Lastly, a small number of exposed cases were observed.

- The association between pesticide exposure, including dicamba, and adult-onset asthma was investigated by Hoppin et al. (2008) in a cross-sectional analysis of female participants of the AHS prospective cohort. The study population consisted of female participants enrolled in the AHS (n = 25,814) who completed study enrollment questionnaires (1993 – 1997) that included questions on pesticide usage and physician's diagnosis of asthma. Cases of self-reported physician-diagnosed asthma as an adult (> 19 years old), were subdivided into atopic or nonatopic asthma based on self-reported eczema and/or hay fever. Pesticide use information collected from the enrollment questionnaires was used to determine lifetime total years of pesticide use and frequency of pesticide application. Polytomous logistic regression was used to calculate ORs and 95% CIs for the association between specific pesticides and asthma, adjusting for age, state, smoking status, BMI, and whether the participant grew up on a farm. Among the 25,814 females included in the analysis, 702 reported adult-onset asthma (282 atopic asthma, 420 nonatopic asthma) and 25,112 participants reported that they did not have asthma. Among the 282 atopic and 420 nonatopic asthma cases, 11 (4.0%) and 13 (3.0%) reported ever use of dicamba, respectively. And, among the 25,112 control subjects, 1,014 (4.0%) reported ever use of dicamba. No evidence of a significant positive association

was reported for dicamba exposure and atopic asthma among farm women, based on ever use (OR = 1.11: 95% CI: 0.60, 2.05; with n = 11 exposed cases) and no evidence of a positive association was reported for nonatopic asthma, based on dicamba ever use (OR = 0.74; 95% CI: 0.42, 1.30; with n = 13 exposed cases).

The overall quality of the study was ranked low based on the study quality criteria provided in the OPP Framework. The cross-sectional study design was a main limitation since temporality of exposure in relation to the outcome could not be determined. Additionally, the study relied on self-report of the outcome. We note a small number of exposed cases (n = 11 - 13) for non-atopic and atopic asthma.

- In a separate study on male farmers, Hoppin et al. (2009) investigated the association between pesticide exposure including dicamba, and adult-onset asthma among male private pesticide applicators using a cross-sectional analysis of data from the AHS prospective cohort. Cases included male private pesticide applicators in the AHS, aged ≥ 20 years, who self-reported physician-diagnosed asthma with onset after 19 years old on the self-administered questionnaires completed at enrollment and shortly thereafter (1993-1997). Cases were subdivided into atopic asthma (those reporting history of physician-diagnosed hay fever or eczema) and nonatopic asthma (no history of physician-diagnosed hay fever or eczema). Pesticide exposure (ever use and IWLD of use) was assessed using data collected on the enrollment questionnaires. Polytomous logistic regression was used to calculate ORs and 95% CIs to evaluate the association between pesticide exposure and adult-onset asthma, adjusting for age, state of residence, smoking, BMI, and high pesticide exposure events (pesticide poisoning). Among the 19,704 private pesticide applicators included in this analysis, 441 reported asthma (n = 127 atopic asthma cases and n = 314 nonatopic asthma cases) and 19,263 reported no history of asthma. 71 (59%) of the 127 atopic asthma cases and 173 (61%) of the 314 nonatopic asthma cases reported dicamba exposure. Among those who reported no history of asthma (n = 19,263), 9,607 (53%) reported exposure to dicamba. No evidence of a significant positive association was reported for atopic asthma based on ever/never dicamba use (OR = 1.19; 95% CI: 0.78, 1.81; with n = 71 exposed cases). And, no evidence of a significant positive association was reported for nonatopic asthma, based on ever/never dicamba use (OR = 1.28; 95% CI: 0.97, 1.69; with n = 173 exposed cases).

  In an exposure-response analysis using the median as the cut-point of dicamba intensity-adjusted exposure to create two exposure categories (1 – 166 days and > 166 days), evidence of a significant positive association was reported for the lowest exposure category for non-atopic asthma (OR = 1.41; 95% CI: 1.03, 1.92; with n = 94 exposed cases) and no evidence of a significant positive association was reported for the highest exposure category (OR = 1.21; 95% CI: 0.87, 1.68; with n = 77 exposed cases) or evidence of an exposure-response trend (p-trend = 0.25). No evidence of a significant positive association was reported for either exposure category of atopic asthma (1.14 < OR < 1.29; all 95% CIs encompassed the null value of 1.0; with n = 32 – 38 cases per exposure category; p-trend = 0.59). In an additional analysis, controls with allergy (atopy) were excluded from the comparison group to determine if the difference in the reported results for atopic and non-atopic asthma was due to atopy alone. No evidence of a significant positive association was reported for dicamba exposure and atopic and non-atopic asthma (*atopic asthma* – OR = 1.20; 95% CI: 0.79, 1.82; with n = 71 exposed cases; *nonatopic asthma* – OR = 1.29; 95% CI: 0.98, 1.70; with n = 173 exposed cases) when allergic individuals were removed from the control group. And, no evidence of a significant positive association was reported for atopy alone (OR = 1.10; 95% CI: 0.98, 1.23; with n = 880 exposed cases). Finally, to determine if the results were due to another co-morbid respiratory disease or asthma, those with chronic bronchitis and farmer's lung were excluded from the analysis. No evidence of a significant positive association was reported for *atopic* asthma (OR = 1.07; 95% CI:

0.64, 1.79; with n = 43 exposed cases) and for *nonatopic* asthma (OR = 1.13; 95% CI: 0.81, 1.59; with n = 105 exposed cases).

The overall quality of the study was ranked low based on the study quality criteria provided in the OPP Framework. The cross-sectional study design was a main limitation since temporality of exposure in relation to the outcome could not be determined. Additionally, the study relied on self-report of the outcome.

- Henneberger et al. (2014) investigated pesticide usage, including dicamba and asthma exacerbation among asthmatic pesticide applicators (commercial and private) enrolled in the AHS. The study population consisted of pesticide applicators living in Iowa and North Carolina who completed both enrollment questionnaires of the AHS study (1993 – 1997) and self-reported physician-diagnosed active asthma.[60] Cases included those participants with active asthma who also reported exacerbation of asthma on the enrollment questionnaire.[61] Current (used in the 12 months before enrollment) and former (used in the past but not in the 12 months before enrollment) pesticide exposure was assessed for chlorothalonil using data from the self-administered questionnaires completed at enrollment. Logistic regression was used to calculate ORs and 95% CIs for the association between dicamba and asthma exacerbation, adjusting for age (years), state of residence, ever smoked, allergic status, and adult onset of asthma, in addition to separate indicator variables for current and past exposure. Among the 926 pesticide applicators with active asthma, 125 of the 202 participants with asthma exacerbation reported dicamba exposure, and 438 of the 724 pesticide applicators without asthma exacerbation reported exposure to dicamba. No evidence of a positive association was reported between dicamba exposure and asthma exacerbation (OR = 1.00; 95% CI: 0.60, 1.60; with n = 125 exposed cases).

  The quality of the study was ranked low based on the study quality criteria provided in the OPP Framework. The cross-sectional study design was a main limitation since temporality for exposure in relation to the outcome could not be determined. Additionally, the study relied on self-report of the outcome.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and asthma. Four available AHS studies (Weselak et al., 2007; Hoppin et al., 2008; Hoppin et al., 2009; Henneberger et al., 2014) examined the association between dicamba exposure and asthma. Weselak et al. (2007) reported no evidence of a positive association between exposure to dicamba during pregnancy and offspring with asthma among the Ontario Farm Family Health Study participants in Canada. The study was ranked moderate quality and was limited by the retrospective approach to gathering information on both the outcome and the exposure, the self-reported outcome without clinical confirmation, and potential for recall bias. The three additional studies examined the association between dicamba exposure and asthma among adults in the AHS prospective cohort in Iowa and North Carolina. Hoppin et al. (2008) reported no evidence of a significant positive association between dicamba exposure and atopic asthma among farm women, based on ever use and no evidence of a positive association for non-atopic asthma, based on dicamba ever use. Hoppin et al. (2009) reported no evidence of a significant

[60] Active asthma was defined as "at least one episode of wheezing or whistling in the past 12 months" and "having breathing problems in the same time period." (Henneberger et al., 2014)
[61] Exacerbation of asthma was defined as a "self-reported visit to a hospital emergency room or doctor for an episode of wheezing or whistling during the past 12 months." (Henneberger et al., 2014)

positive association between ever use of dicamba and adult-onset atopic and non-atopic asthma among male farmers in the AHS. And finally, Henneberger et al. (2014), evaluated asthma exacerbation among asthmatic pesticide applicators in the AHS and reported no evidence of a positive association between exacerbated asthma and current dicamba exposure. The quality of each of the three AHS studies was ranked low due to the cross-sectional study design as temporality for exposure in relation to the outcome could not be determined. Additionally, the studies relied on self-report of the outcome.

Chronic bronchitis:

Three publications (Weselak et al., 2007; Hoppin et al., 2007; Valcin et al., 2007) examined the association between dicamba exposure and chronic bronchitis.

- Weselak et al. (2007) investigated the potential association between pesticide exposures including dicamba among farm couples and respiratory effects and allergies in their offspring. The study population was part of the Ontario Farm Family Health Study (OFFHS). Weselak et al. (2007) analyzed farm couple's various exposures during pregnancy including pesticide exposure and respiratory effects (asthma bronchitis, persistent cough or bronchitis) and hay fever or allergies. Three questionnaires were mailed to participants, one for each the husband, wife, and the farm pesticide applicator if different form either the husband or wife. Wives were asked to report a full reproductive history of their first five pregnancies and their health outcome, as well as if a doctor had ever told them that their child had any of the following health conditions: asthma, chronic bronchitis or cough, and hayfever or allergies. For the exposure assessment, data was pooled from questionnaires completed by the wife and the husband, in addition to a farm applicator if separate from the husband or wife. Exposure questionnaires reported on exposure details regarding pesticide applications, with the addition of a direct chemical activities assessment. Logistic regression was used to calculate ORs and corresponding 95% CIs for the association between dicamba exposure and the mentioned health conditions, adjusting for specific covariates within each analysis. Dicamba models were adjusted for Among the total number of offspring (n = 3,405) in this study, parental exposure to dicamba during pregnancy (month of conception up to the month of delivery) was reported for 282 of the total 2,243 exposed offspring and of those exposed to dicamba, 10 reported asthma, 9 reported chronic bronchitis or cough, and 19 reported hayfever or allergies. For the analysis that examined the associaiton between dicamba exposure during pregnancy and chronic bronchitis or cough in offspring, no evidence of a significant positive association was reported for dicamba exposure during pregnancy and chronic bronchitis or cough among offspring (compared to pregnancies with no reported pesticide use during pregnancy (Crude OR = 1.20; 95%CI: 0.52, 2.79; with n = 9 exposed cases). When adjusted for child's age at time of questionnaire, fathers age at conception, and income, covariates that when added to the crude model changed the exposure OR by 10% or more, no evidence of a significant positive association was reported (OR = 1.66; 95% CI: 0.58, 4.80; with n=19 exposed cases).

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  Overall Weselak et al. (2007) was considered moderate quality based on the Framework. Despite being a population-based cohort study, exposure and outcome information were both gathered retrospectively by self-report without any corroboration pesticide use data or confirmation of outcome by medical record abstraction. Since dosing information was not provided in this study, the degree of exposure for each study subject was unknown and could have potentially led to misclassification. Also, because several couples included within the study were reporting on several past pesticide exposures and past pregnancies, and assuming some pregnancies led to poor outcomes (i.e. abortions), recall bias could have occurred and ultimately affected the woman's behavior for future

pregnancies and couples' memory of pesticide exposure. Lastly, a small number of exposed cases were observed.

- Hoppin et al. (2007) evaluated the potential association between exposure to pesticides including chlorothalonil and chronic bronchitis among pesticide applicators in a cross-sectional analysis of the AHS prospective cohort. The study population (n = 20,908) included male pesticide applicators enrolled in the AHS cohort living in Iowa or North Carolina who completed both the enrollment questionnaire and the mailed questionnaire shortly after enrollment (1993 – 1997). Prevalent cases included private pesticide applicators (males only) who self-reported a physician diagnosis of chronic bronchitis at > 19 years of age on the mailed questionnaire completed shortly after enrollment. Pesticide exposure was assessed using responses collected on the enrollment questionnaire. Base logistic regression was used to calculate ORs and 95% CIs to estimate the association between chlorothalonil ever/never exposure and chronic bronchitis, adjusting for state of residence, age, gender, and pack years smoking. Among the 654 cases and 20,254 non-cases included in the analysis, 48% of cases (n = ~313 - 314) and 53% of non-cases (n = ~10,734 – 10,735) reported exposure to dicamba. No evidence of a positive association was reported between dicamba exposure and chronic bronchitis among male pesticide applicators (OR = 1.00; 95% CI: 0.83, 1.21; with n = ~313 - 314 exposed cases and n = ~10,734 – 10,735exposed non-cases).

  The overall quality of the study was ranked low based on the study quality criteria provided in the OPP Framework. The cross-sectional study design was a main limitation since temporality for exposure in relation to the outcome could not be determined. Additionally, the study relied on self-report of the outcome.

- In a separate study, Valcin et al. (2007) investigated occupational risk factors for chronic bronchitis, including exposure to dicamba and other pesticides, among women by conducting a cross-sectional analysis of the AHS prospective cohort. The 21,541 study participants included non-smoking female spouses of pesticide applicators enrolled in the AHS who completed the spouse questionnaire shortly after enrollment (1993 - 2000). Cases of physician diagnosed chronic bronchitis when ≥20 years old were self-reported by participants on the spouse questionnaire completed shortly after enrollment. In addition to health outcome information, the self-administered spouse questionnaire also included detailed information on pesticide exposures and potential confounders. Logistic regression was used to calculate ORs and 95% CIs for lifetime days of exposure to specific pesticides, including dicamba, adjusting for age and state of residence and further adjusted for additional variables within each chemical class. Of the 583 cases, 5% (n ~ 29 - 30) reported chlorothalonil exposure, while 4% (n = ~838 - 839) of the 20,958 controls reported exposure. No evidence of a significant positive association was reported between dicamba and chronic bronchitis (OR = 1.39; 95% CI: 0.92, 2.10; with n = 29 - 30 exposed cases). When the model was further adjusted to account for exposure to other herbicides[62] in addition to age and state of residence, the magnitude of the non-significant association was attenuated (OR = 1.12; 95% CI: 0.64, 1.95; with n = 29 - 30 exposed cases) when adjusted for age, state of residence, and exposure to other herbicides.

  The overall quality of the study was ranked low based on the study quality criteria provided in the OPP Framework. The cross-sectional study design was a main limitation since temporality for

[62] The authors did not explicitly state which pesticides but said, "After adjusting for the all pesticides in their respective groups, some associations were attenuated."

exposure in relation to the outcome could not be determined. Additionally, the study relied on self-report of the outcome.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and chronic bronchitis. Three publications (Weselak et al., 2007; Hoppin et al., 2007; Valcin et al., 2007) examined the association between dicamba exposure and chronic bronchitis among agricultural populations. Weselak et al. (2007) reported no evidence of a significant positive association between dicamba exposure during pregnancy and chronic bronchitis in offspring in the Ontario Farm Family Health Study in Canada. The study was ranked moderate quality and was limited by the retrospective approach used to gather both exposure and outcome information. The two remaining studies were conducted among the AHS prospective cohort. Hoppin et al. (2007) reported no evidence of a significant positive association between dicamba exposure and chronic bronchitis among male pesticide applicators in the AHS based on ever use. Valcin et al. (2007) reported no evidence of a significant positive association between chronic bronchitis and dicamba in their analysis of female spouses of AHS pesticide applicators. Both Hoppin et al. (2007) and Valcin et al. (2007) used cross-sectional study designs. As such, the studies were unable to assess the temporal association between dicamba exposure and chronic bronchitis and were of low quality based on the study quality criteria outlined in the OPP framework.

Rhinitis

One AHS study (Slager et al., 2010) examined the association between dicamba exposure and rhinitis.

Slager et al. (2009) investigated the association between exposure to pesticides, including dicamba, and current rhinitis through a cross-sectional analysis of the commercial pesticide applicators in the AHS prospective cohort. A total of 2,245 commercial pesticide applicators from Iowa completed the self-administered questionnaire at enrollment (1993 – 1997) and 46% of those completed the self-administered mail-in questionnaire shortly after enrollment. The outcome of current rhinitis (a stuffy, runny, or itchy nose in the past 12 months) along with additional medical history was reported on the questionnaire administered shortly after enrollment. Pesticide exposure, ever use and lifetime exposure, was assessed using responses from both the enrollment questionnaire and the mail-in questionnaire completed shortly after. Logistic regression models were used to calculate ORs and 95% CIs to analyze the association between ever use of dicamba and current rhinitis, adjusting for age, education, and growing up on a farm. Of the 1,664 cases of rhinitis reported in the study group, 568 (35%) reported exposure to dicamba; and, among the 581 respondents who reported no current rhinitis, 165 (29%) reported exposure to dicamba. No evidence of a significant positive association was reported between exposure to dicamba and current rhinitis based on ever use (OR = 1.18; 95% CI: 0.95, 1.47). The investigators examined the exposure-response relationship by assessing the following exposure categories: 1-4 days per year, 5-9 days per year, and 10-19 days per year, 20-39 days per year, 40-59 days per year, and $\geq$60 days per year. No evidence of significant positive exposure was reported for any exposure category and no evidence of an exposure-response relationship ($1.03 < OR < 1.66$; all 95% CIs encompassed the null value 1.0; with n = 49 - 150 cases per exposure category; p-trend = 0.189).

The quality of the study was ranked low based on the OPP Framework. While the study benefited from the strength of the AHS exposure assessment, the cross-sectional study design was a main limitation since temporality for exposure in relation to the outcome could not be determined. Additionally, the study relied on self-report of the outcome.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and rhinitis. One available study (Slager et al., 2010) examined rhinitis among commercial pesticide applicators in the AHS and reported no evidence of a significant positive association based on ever use and on lifetime days of use and no evidence of an exposure-response. The overall quality of the study was ranked low due to the cross-sectional study design since temporality for exposure in relation to the outcome could not be determined. Additionally, the study relied on self-report of the outcome.

Wheeze

Four AHS studies (Hoppin et al., 2002; Hoppin et al., 2006a; Hoppin et al., 2006b; Hoppin et al., 2017) examined the association between dicamba exposure and wheeze.

- Hoppin et al. (2002) evaluated the association between exposure to pesticides, including dicamba, and the prevalence of wheeze among pesticide applicators in a cross-sectional analysis of the AHS prospective cohort. The study population consisted of 20,468 pesticide applicators living in Iowa and North Carolina enrolled in the AHS, who completed both the enrollment questionnaires (1993 – 1997). Wheeze in the past year and pesticide exposure were self-reported on the self-administered questionnaires completed at enrollment and shortly following enrollment. Logistic regression was used to estimate the association between dicamba ever use and wheeze in the past year, adjusting for age, state, past smoking, current smoking, and asthma/atopy. Of the 20,468 participants included in the analysis (3,838 reported wheeze and 16,630 reported no wheeze) 30.8% (n = ~1,182 – 1,183) of those with wheeze reported exposure to dicamba and 32.3% (n ~ 5,371 – 5,372) of those who reported no wheeze also reported exposure to dicamba. No evidence of a significant positive association between dicamba exposure and wheeze among pesticide applicators (OR = 1.06; 95% CI: 0.75, 1.16) based on ever use in the past year. Further, the authors reported no evidence of a linear (monotonic) trend across categories based on five ordinal categories of exposure (p-trend = 0.22).

  The quality of the study was ranked low based on the study quality criteria outlined in the OPP framework. Hoppin et al. (2002) relied on a cross-sectional design that assessed the relationship between prevalent cases of wheeze and pesticide exposure. As such, the study was unable to assess temporal association between DDVP exposure and wheeze.

- In a separate AHS study, Hoppin et al. (2006a) investigated the association between pesticides including chlorothalonil, and the prevalence of wheeze using a cross-sectional analysis of the AHS prospective cohort. Study participants included private pesticide applicators (n = 17,920) and commercial pesticide applicators (n = 2,255) enrolled in the AHS between 1993 – 1997. Cases of wheeze were defined as participants who reported episodes of wheezing or whistling in the chest in the year before study enrollment were self-reported on the enrollment questionnaire. Pesticide exposure (ever use in the year before enrollment) was reported on the enrollment questionnaire. Among the total study participants, 19% of the 17,920 private applicators and 22% of the 2,255 commercial applicator study participants reported wheeze in the past year. Among private applicators, 46%, 32%, and 22% reported never, former, or current use of dicamba, and among commercial applicators, 40%, 26%, and 34% reported never, former, or current use of dicamba, respectively. Logistic regression was used to estimate ORs and 95%CIs for the association between dicamba and wheeze, adjusted for age, BMI, smoking, asthma/atopy, and previous use of pesticides. State of residence was also included as a potential confounder in the analyses for farmer applicators only; commercial applicator participants resided only in Iowa. Chlorimuron-ethyl adjustment was included

in models for commercial applicators. No evidence of a significant positive association was reported between current dicamba use and wheeze among private pesticide applicators (OR = 1.05; 95% CI: 0.93, 1.18) and no evidence of a positive association was reported among commercial applicators (OR = 0.78; 95% CI: 0.58, 1.07). Additional numeric details for commercial applicators were described in a separate publication (Hoppin et al., 2006b).

The quality of the study was ranked low based on the study quality criteria outlined in the OPP framework. Hoppin et al. (2006a) relied on a cross-sectional design that assessed the relationship between prevalent cases of wheeze and pesticide exposure. As such, the study was unable to assess the temporal association between dicamba exposure and wheeze.

- The results for commercial applicators are described in more detail in an additional AHS study, Hoppin et al. (2006b). Among the 486 commercial applicators that reported wheeze in the past year, 190 (40%) reported never use, 123 (26%) former use, and 167 (35%) reported current use of dicamba. No evidence of a significant positive association was reported for current use of dicamba and wheeze in the past year (OR = 1.11; 95% CI: 0.86, 1.43; with n = 167 exposed cases and n = 569 exposed non-cases).

  The study was determined to be of low quality based on the study quality criteria outlined in the OPP framework. Hoppin et al. (2006b) relied on a cross-sectional design that assessed the relationship between prevalent cases of wheeze and pesticide exposure. As such, the study was unable to assess temporal association between dicamba exposure and wheeze.

- Hoppin et al. (2017) investigated the association between pesticide exposure including dicamba, and allergic and non-allergic wheeze among male private pesticide applicators through a cross-sectional analysis of the AHS prospective cohort. The study population (N=22,134) consisted of male private pesticide applicators who completed the AHS enrollment (1993 - 1997) and follow-up questionnaires (2005 – 2010) (n = 22,134) and reported symptoms of wheeze. Wheeze was defined as at least one episode of wheeze or whistling in the chest in the past year with a physician-diagnosis of hay fever for allergic wheeze, or as at least one episode of wheeze or whistling in the chest in the past year without a diagnosis of hay fever for non-allergic wheeze. Controls were participants without wheeze but could have had allergy as authors reported they were interested in allergy as a modifier of wheeze not as an outcome. Pesticide exposure data reported at enrollment and follow-up was used to create three definitions for exposure current use (since the last AHS interview), past use (not used since the last AHS interview), and never use of dicamba. Additionally, frequency and duration of use information was captured for a subset of pesticides. Polytomous logistic regression was used to determine the association between wheeze and dicamba exposure, and allergic and non-allergic wheeze were investigated separately. Models were adjusted for age, BMI, state, smoking, and current asthma, as well as for days spent applying pesticides and days driving diesel tractors. Among the 1,310 allergic wheeze cases, 13% reported current use of dicamba, and among the 3,939 non-allergic wheeze cases, 15% reported current use of dicamba. Of the 16,885 control subjects, 12% reported current use of dicamba. Evidence of a positive association was reported between current dicamba use and allergic wheeze (OR = 1.26; 95% CI: 1.04, 1.58; with n = ~170 – 171 exposed cases) and non-allergic wheeze (OR = 1.29; 95% CI: 1.14, 1.45; with n = ~590 – 560 exposed cases).

  A further analysis considered the association between cumulative days of use of dicamba since the last AHS interview and allergic and non-allergic wheeze among male private applicators. Authors divided the distribution of current users of dicamba into the following exposure categories based on frequency of current use: 1-2 days, 3-5 days, 6-7 days, 8-10 days, 11-110 days of dicamba use *in the*

past year. Never use served as the referent category for the analysis. In the exposure-response analysis for allergic wheeze, evidence of a significant positive association was reported for the highest exposure category of dicamba current use, and current wheeze (OR = 2.00; 95% CI: 1.27, 3.16; with n = ~26 - 27 exposed cases). No evidence of a significant positive association was reported for any other exposure category of dicamba and allergic wheeze (1.09 < OR < 1.30; all 95% CIs encompassed the null value of 1.0; with n = ~13 - 66 cases per exposure category). For non-allergic wheeze evidence of a significant positive association was reported in the lowest four exposure categories: 1-2 days, 3-5 days, 6-7 days, 8-10 days (1.11 < OR < 1.44; all 95% CIs encompassed the null value 1.0; with n = 78 - 237 cases per exposure category). No evidence of a significant positive association was reported in the highest exposure category of 11-110 days of use of dicamba in the last year (OR = 1.35; 95% CI: 0.99, 1.85; with n = ~39-40 exposed cases). The authors did not report a p-trend statistic for the exposure-response analysis for either allergic or non-allergic wheeze and dicamba; however, inspection of the ORs associated with each category suggests an exposure-response trend may not exist for either allergic or non-allergic wheeze.

The quality of the study was ranked low based on the study quality criteria outlined in the OPP framework. Hoppin et al. (2017) relied on a cross-sectional design that assessed the relationship between current wheeze and pesticide exposure. As such, the study was unable to assess the temporal association between dicamba exposure and wheeze.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and wheeze. Four AHS studies (Hoppin et al., 2002; Hoppin et al., 2006a; Hoppin et al., 2006b; and Hoppin et al., 2017) examined the association between dicamba exposure and wheeze in the AHS prospective cohort study population. Hoppin et al. (2002), reported no evidence of a significant positive association between dicamba exposure and wheeze among pesticide applicators, based on ever use. Hoppin et al. (2006a) reported no evidence of a significant positive association between current dicamba use and wheeze for farmer (private) applicators, based on ever use within the year before enrollment. Hoppin et al. (2006b), reported no evidence of a significant positive association between current dicamba use and wheeze among commercial applicators, based on ever use. In a fourth study on the AHS that included a cross-sectional analysis of dicamba exposure in the past year and wheeze in the past year using the responses from the 2005-2010 follow-up survey rather than from enrollment, Hoppin et al. (2017) reported evidence of a significant association between dicamba exposure in the past year and non-allergic wheeze in the past year based on ever use. And, evidence of a significant positive association in the three lowest exposure categories of nonallergic wheeze in the exposure-response analysis. No evidence of a significant positive association was reported in the highest exposure category. For allergic wheeze, no evidence of a significant positive association was reported between dicamba and wheeze based on ever use and evidence of a positive association was reported in the highest exposure category of dicamba use in the past year in the exposure-response analysis. The authors did not report a p-trend statistic for the exposure-response analysis for either allergic or non-allergic wheeze and dicamba; however, inspection of the ORs associated with each category suggests an exposure-response trend may not exist for either allergic or non-allergic wheeze. All four studies were ranked low quality, as they relied on a cross-sectional design that was unable to assess the temporality of the relationship between cases of pesticide exposure and wheeze. Additionally, health outcomes were self-reported.

Sleep Apnea

The association between chlorothalonil exposure and sleep apnea was evaluated in one publication (Baumert et al., 2018).

Baumert et al. (2018) evaluated the association between dicamba exposure and sleep apnea in male pesticide applicators using data from the Agricultural Lung Health Study (ALHS), a case-control study of current asthma nested within the AHS cohort. ALHS participants were identified via an AHS follow-up telephone interview (2005 – 2010) and enrolled into the ALHS between 2009 and 2013. Cases of sleep apnea included male pesticide applicators who self-reported physician-diagnosed sleep apnea with treatment on the ALHS computer-assisted telephone survey. The non-cases were randomly selected from the AHS cohort and included study participants who did not self-report physician-diagnosed sleep apnea. AHS exposure questionnaires completed at enrollment (1993 – 1997) and at 5-year and 10-year follow-up time points (1999 – 2003, 2005 – 2010) were used to assess ever use of dicamba. Logistic regression was used to evaluate the association between dicamba ever use and sleep apnea, adjusting for state, age, BMI, history of diabetes, asthma, hypertension, and cardiovascular disease. Among the male pesticide applicators participating in the study, 1,375 (58.5%) of the 234 sleep apnea cases and 736 (55.1%) of the 1,335 non-cases reported exposure to dicamba. No evidence of a significant positive association was reported between dicamba exposure and sleep apnea based on ever/never use (OR = 1.08; 95% CI: 0.76, 1.68).

The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Authors reported that the response rate for enrollment into the ALHS nested case-control study was 50% and this possibly could have introduced selection if there were differences between those that responded and those that did not. This information was not available as sleep apnea was not asked about on the earlier questionnaire. Additionally, cases of sleep apnea with treatment were self-reported allowing the potential for misclassification of the outcome. The outcome assessment would have been strengthened with medical record confirmation.

EPA Conclusion

Overall, there is *no epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and sleep apnea. One study (Baumert et al., 2018) examined the association between dicamba exposure and sleep apnea among male pesticide applicators enrolled in the AHS and reported no evidence of a significant positive association, based on ever use of dicamba. The quality of the study was ranked moderate. As part of the AHS, this study benefited from the strengths of the AHS study cohort including the prospective cohort study design. This was a potential study limitation as the number of incident stroke cases may have been underreported.

Stroke

The association between dicamba exposure and stroke was evaluated in one publication (Rinsky et al., 2013) described below.

Rinsky et al. (2013) examined the association between pesticide exposure, including dicamba, and the risk of stroke mortality among AHS prospective cohort participants. The study population consisted of male pesticide applicators (n = 51,603) enrolled in the AHS living in Iowa and North Carolina. Cases of stroke mortality included AHS study participants who died from a stroke between study enrollment (1993 – 1997) through December 31, 2008, and vital status of each case was ascertained using state death certificates. The non-cases included AHS study participants who did not suffer from stroke mortality.

Pesticide exposure was assessed for 50 different pesticides, including dicamba, using self-administered questionnaires completed at study enrollment. Of the 308 study participants who experienced a fatal stroke, 89 (33%) reported exposure to dicamba; and of the 51,295 controls, 24,932 (51) reported dicamba exposure. HRs and 95% CIs were calculated using Cox proportional hazards analysis, adjusting for smoking status, alcohol intake, and state of residence. No evidence of a positive association was reported between dicamba exposure and stroke mortality (HR = 0.90; 95% CI: 0.68, 1.21) based on ever/never use.

The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. As part of the AHS, this study benefited from the strengths of the AHS study cohort including the prospective cohort study design and case ascertainment. Although the study investigated stroke mortality, details regarding stroke morbidity were not provided. This was a potential study limitation as the number of incident stroke cases may have been underreported.

EPA Conclusion

Overall, there is *no epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and stroke. One study (Rinsky et al., 2013) examined the association between dicamba exposure and stroke among male pesticide applicators enrolled in the AHS and reported no evidence of a positive association between dicamba exposure and stroke mortality. The quality of the study was ranked moderate. As part of the AHS, this study benefited from the strengths of the AHS study cohort including the prospective cohort study design and case ascertainment. Although the study investigated stroke mortality, details regarding stroke morbidity were not provided. This was a potential study limitation as the number of incident stroke cases may have been underreported.

Suicide

One study (Beard et al., 2011) evaluated the potential relationship between dicamba exposure and suicide.

Beard et al. (2011) evaluated the potential association between pesticide exposure including dicamba and suicide among pesticide applicators and their spouses in the AHS prospective cohort. Cases of suicide that occurred after enrollment (1993-1997) through May 2009 were identified by linking the AHS cohort to state mortality files and the National Death Index. Pesticide exposure was assessed via a self-administered questionnaire at enrollment. Cox proportional hazards models were used to analyze the association between dicamba ever exposure and suicide risk to calculate HRs and 95% CIs, adjusting for age at enrollment, sex, number of children, frequency of alcohol consumption within the past year, and smoking. Among the study population (n = 81,998), 26,363 reported exposure to dicamba. Among the 110 cases of suicide that occurred between enrollment (from 1993 to 1997) and May 2009, 33 cases reported ever exposure to dicamba. No evidence of a positive association was reported between dicamba exposure and suicide (HR = 0.63; 95% CI: 0.41, 0.98) based on ever/never use. A further analysis considered cumulative lifetime days of use of dicamba and the risk of suicide among applicators with the specific cut points around median lifetime days of use for dicamba at ≤ 39 days and > 39 days. No evidence of a positive association was reported for dicamba exposure at either exposure level (*≤ 39 days of use* – HR: 0.49; 95% CI: 0.27, 0.88; with n = 14 cases; *> 39 days of use* – HR: 0.67; 95% CI: 0.37, 1.19 with n = 15 cases; p-trend = 0.24).

The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths include the prospective design of AHS and the detailed exposure assessment approach. The study was also able to identify suicide cases using the National Death Index. This approach may be comprehensive for suicide cases resulting in mortality but provides incomplete characterization of

suicidal behavior because cases of suicide attempt and ideation cannot be identified using the National Death Index.

EPA Conclusion

Overall, there is *no epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and suicide. One AHS study (Beard et al., 2011) examined the association between dicamba exposure and suicide and reported no evidence of a positive association among pesticide applicators. The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths included the prospective design of the AHS and the AHS detailed exposure assessment approach. The study was also able to identify suicide cases using the National Death Index. This approach may be comprehensive for suicide cases resulting in mortality but provides incomplete characterization of suicidal behavior because cases of suicide attempt and ideation cannot be identified using the National Death Index.

Thyroid disease

Six studies (Goldner et al., 2010. Goldner et al., 2013; Shrestha et al., 2018b; Shrestha et al., 2018c; Shrestha et al., 2019; Lerro et al., 2018) investigated the association of dicamba exposure and thyroid disease including hyperthyroid disease, hypothyroid disease, and other thyroid disease.

Hyperthyroid disease

Three studies (Goldner et al., 2010; Shrestha et al., 2018b; Shrestha et al., 2019) investigated the association between dicamba exposure and hyperthyroid disease.

- Goldner et al. (2010) evaluated the association between prevalent thyroid disease and dicamba and other pesticides among female spouses of male private applicators in a cross-sectional analysis of data from the AHS prospective cohort. The study population included all female spouses of male private applicators who completed both the enrollment questionnaire on pesticide exposure (1993 – 1997) and the follow-up telephone interview collecting information on history of thyroid disease (1999 – 2003) and had complete data on all covariates. Cases of physician-diagnosed thyroid disease were ascertained through self-report during follow-up interviews (1999 – 2003) and were further classified into three subgroups: hypothyroidism, hyperthyroidism, and other thyroid disease. Pesticide exposure among female spouses of male private applicators was reported through the Spouse Enrollment Questionnaire given at enrollment (1993 – 1997) and included direct pesticide exposure (ever use of dicamba), but not indirect pesticide exposure of the spouse (husband's use of the pesticide). Polytomous logistic regression was used to analyze the association between ever use of dicamba and the occurrence of thyroid disease, adjusting for BMI, age at enrollment, smoking status, hormone replacement therapy (ever/never), and education. Among the 2,043 total cases of thyroid disease reported among female spouses, there were 17 (4.6%) hyperthyroid cases, 27 (2.4%) hypothyroid cases, and 19 (3.40%) 'other' thyroid cases reported ever use of dicamba. No evidence of a significant positive association was reported for the association between dicamba exposure (ever use) and hyperthyroid disease among female spouses of pesticide applicators (OR = 1.30; 95% CI: 0.79, 2.10; with n = 17 exposed cases).

  The study quality was ranked low based on the study quality criteria provided in the OPP Framework. Authors were not able to analyze incident cases separately from prevalent cases due to the way the data were collected. The cross-sectional study design was a limitation since temporality for exposure

in relation to the outcome could not be determined. Reliance on self-report of the outcome without clinical confirmation was another limitation. Additionally, the investigators were only able to assess ever/never exposure and did not have more detailed exposure information to assess cumulative dicamba exposure.

- Shrestha et al. (2018b) evaluated the association between exposures to pesticides including dicamba and incident thyroid disease. The study population consisted of female spouses of pesticide applicators enrolled in the AHS, an ongoing, prospective cohort study. Hyperthyroid and hypothyroid disease status was ascertained through self-report during follow-up interviews during Phase II (1999 – 2003), Phase III (2005 – 2010) and Phase IV (2013 – 2016) of the study. Validation of self-reported cases of hyperthyroid and hypothyroid disease was carried out using medical record data; however, study authors reported that for hyperthyroid disease, only 32% of the study participants who self-reported hyperthyroid disease confirmed their diagnosis using medical record confirmation and thyroid disease. Pesticide exposure was reported through self-administered questionnaires at enrollment (1993 – 1997). The Cox proportional hazards model was used to calculate separate HRs for hypothyroid and hyperthyroid disease, controlling for smoking, education, and state and then all mentioned with correlated pesticides. Authors restricted their analysis to exposures with at least 10 thyroid disease cases in each exposure category for all but stricter case analysis for which at least 5 exposed cases in each exposure category were required. For this analysis, the study population included 24,092 AHS female spouses. Authors used multiple imputation with fully conditional specification method to impute missing covariates for 1,273 spouses missing information on smoking status and 3,106 on education. Authors created five imputed datasets, performed regression analysis in each dataset, and obtained the pooled parameter estimates. For hyperthyroid disease, no evidence of a significant positive association was reported for dicamba exposure (HR: 1.35; 95% CI: 0.91, 1.99 with n = 27 exposed cases, 477 unexposed cases) based on ever use. When correlated pesticides were adjusted for in addition to state, education and smoking, no evidence of a significant positive association was reported (HR: 1.11; 95% CI: 0.66, 1.86 with n = 27 exposed cases, 477 unexposed cases). An additional analysis that only included thyroid cases as defined by receipt of treatment in AHS spouses, reported no evidence of a significant positive association between dicamba exposure and hyperthyroid disease (HR: 1.40; 95% CI: 0.91, 2.17 with n = 22 exposed cases, 368 unexposed cases). And finally, an additional analysis that only included thyroid cases as defined by those confirmed by medical records or validation questionnaire, reported no evidence of a significant positive association between dicamba exposure and hyperthyroid disease female spouses of pesticide applicators (HR: 1.44; 95% CI: 0.78, 2.67 with n = 11 exposed cases, 175 unexposed cases).

  The study quality was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths included the prospective cohort design, and the extensive methods used to obtain exposure information for several pesticides including dicamba. Study limitations included self-reported outcome by the study participants and potential selection bias. Since thyroid disease was self-reported in this study (only 32% of the self-reported cases were ascertained via medical records), it was likely some cases misclassified their thyroid disease status and subtype. Potential selection bias was likely if study subject participation in the follow-up phases was related to their disease status for hyperthyroidism. Additional study details regarding frequency and duration of pesticide use for dicamba would have been useful but were not provided.

- Shrestha et al. (2019) evaluated the association between incident hyperthyroid disease and exposures to pesticides including dicamba. The study population consisted of private pesticide applicators enrolled in the AHS, an ongoing, prospective cohort study. Pesticide exposure was reported through self-administered questionnaires at enrollment (1993 – 1997), and hyperthyroid disease status was ascertained through self-report during follow-up interviews during Phase II (1999 – 2003), Phase III

(2005 – 2010) and Phase IV (2013 – 2016) of the study. Cases of hyperthyroid disease were validated using medical record data or two validation questionnaires. Validation by medical records was accomplished among only 32% of self-reported cases. The Cox proportional hazards model was used to calculate HRs for hyperthyroid disease, adjusting for smoking, education, state, and sex. Authors restricted their analysis to exposures with at least 10 thyroid disease cases in each exposure category in the overall analysis, but for the stricter case analysis,[63] at least 5 exposed cases in each exposure category were required due to the limited sample size. No evidence of a positive association between dicamba and hyperthyroidism among private applicators was reported in the overall analysis (n = 35,150) (HR: 0.74; 95% CI: 0.55,1.00), with n = 100 exposed cases). Authors did not report results for the analysis with the stricter case definition. An additional sub-analysis that investigated the association between dicamba exposure (based on ever/never use) and hyperthyroid risk among private applicators when females were excluded (n = 34,375) found no evidence of a positive association (HR: 0.76; 95% CI: 0.56, 1.03, with n = 98 exposed cases). In an additional analysis that adjusted for correlated pesticides (Spearman correlation coefficient ≥ 0.40), no evidence of a positive association was reported for dicamba and hyperthyroid disease when additionally adjusted for the correlated pesticide imazethapyr (HR: 0.72; 95% CI: 0.53, 0.98)

This study was ranked moderate according the study quality criteria in the OPP Framework. Strengths of the AHS as noted above, including the prospective study design and pesticide-use information. The study was limited by the reliance on self-report of hyperthyroidism diagnosis even though they attempted to validate cases via medical records (32% confirmed by medical personnel), and the pesticide use information was limited to use prior to enrollment and did not account or pesticide use that occurred after enrollment and may have led to exposure misclassification.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and hyperthyroid disease. Three publications (Goldner et al., 2010. Shrestha et al., 2018b; Shrestha et al., 2019) examined the relationship between dicamba exposure and hyperthyroid disease among AHS study participants. Goldner et al. (2010) reported no evidence of a significant positive association between dicamba ever use and hyperthyroid disease among female spouses of pesticide applicators enrolled in the AHS. The publication was ranked low due to a cross-sectional study design since temporality for exposure in relation to the outcome could not be determined and was limited by self-reported outcome. Shrestha et al. (2108b) also reported no evidence of a significant positive association among female spouses of pesticide applicators in the AHS, based on dicamba ever use and longer follow-up time and was ranked moderate quality. A third publication (Shrestha et al., 2019) reported no evidence of a positive association among private pesticide applicators in the AHS based on dicamba ever use and was ranked moderate quality. Both Shrestha et al. (2018b) and Shrestha et al. (2019) attempted to validate the self-reported hyperthyroidism diagnosis via medical record confirmation, however only 32% of attempted cases were ultimately clinically confirmed. Potential selection bias was also likely if study subject participation in the follow-up phases was related to their disease status for hyperthyroidism. An additional limitation of all three publications was that only ever use of pesticides prior to enrollment was captured rather than pesticide use that occurred after enrollment and this may have led to exposure misclassification.

[63] In this study, the stricter case definition was inclusive of a.) cases confirmed via medical records or validation questionnaire; or, b.) cases who reported having hyperthyroidism ≥ 2 times on validation surveys.

Hypothyroid disease

Five studies (Goldner et al., 2010; Goldner et al., 2013; Shrestha et al., 2018b; Shrestha et al., 2018c; Lerro et al., 2018) investigated the association of dicamba exposure hypothyroid disease.

- Goldner et al. (2010) evaluated the association between prevalent thyroid disease and dicamba and other pesticides among female spouses of male private pesticide applicators in a cross-sectional analysis of data from the AHS prospective cohort. The study population included all female spouses of male private applicators who completed both the enrollment questionnaire on pesticide exposure (1993 – 1997) and the follow-up telephone interview collecting information on history of thyroid disease (1999 – 2003) and had complete data on all covariates. Cases of physician-diagnosed thyroid disease were ascertained through self-report during follow-up interviews (1999 – 2003) and were further classified into three subgroups: hypothyroidism, hyperthyroidism, and other thyroid disease. Pesticide exposure among female spouses of male private applicators was reported through the Spouse Enrollment Questionnaire given at enrollment (1993 – 1997) and included direct pesticide exposure (ever use of dicamba), but not indirect pesticide exposure of the spouse (husband's use of the pesticide). Polytomous logistic regression was used to analyze the association between ever use of dicamba and the occurrence of thyroid disease, adjusting for BMI, age at enrollment, smoking status, hormone replacement therapy (ever/never), and education. Among the 2,043 total cases of thyroid disease reported among female spouses, there were 17 (41.6%) hyperthyroid cases, 27 (2.4%) hypothyroid cases, and 19 (3.4%) 'other' thyroid cases reported ever use of dicamba. No evidence of a positive association was reported for the association between dicamba exposure and hypothyroid disease (OR = 0.66; 95% CI: 0.45, 0.98; with n = 27 exposed cases).

  The study quality was ranked low based on the study quality criteria provided in the OPP Framework. Authors were not able to analyze incident cases separately from prevalent cases due to the way the data were collected. The cross-sectional study design was a limitation since temporality for exposure in relation to the outcome could not be determined. Reliance on self-report of the outcome without clinical confirmation was another limitation. Additionally, the investigators were only able to assess ever/never exposure and did not have more detailed exposure information to assess cumulative dicamba exposure.

- Shrestha et al. (2018b) evaluated the association between thyroid disease and exposures to pesticides including dicamba. The study population consisted of female spouses of pesticide applicators enrolled in the AHS, an ongoing, prospective cohort study. Pesticide exposure was reported through self-administered questionnaires at enrollment (1993 – 1997), and thyroid disease, both hyperthyroid and hypothyroid disease status, was ascertained through self-report during follow-up interviews during Phase II (1999 – 2003), Phase III (2005 – 2010) and Phase IV (2013 – 2016) of the study. Validation of self-reported cases of hyperthyroid and hypothyroid disease was carried out using medical record data. The Cox proportional hazards model was used to calculate separate HRs for hypothyroid and hyperthyroid disease, controlling for smoking, education, and state. Authors restricted their analysis to exposures with at least 10 thyroid disease cases in each exposure category for all but the stricter case analysis for which at least 5 exposed cases in each exposure category were required. For this analysis, the study population included 24,092 AHS female spouses. Authors used multiple imputation with fully conditional specification method to impute missing covariates for 1,273 spouses missing information on smoking status and 3,106 on education. Authors created five imputed datasets, performed regression analysis in each dataset, and obtained the pooled parameter estimates. For hypothyroid disease, no evidence of a positive association was reported for dicamba exposure (HR: 0.90; 95% CI: 0.70, 1.16; with n = 63 exposed cases, 1,480 unexposed cases). No evidence of a significant positive association was reported between dicamba exposure and hypothyroid disease

when further adjusted for correlated pesticides (HR: 1.17; 95% CI: 0.85, 1.60; with n = 63 exposed cases, 1,480 unexposed cases). An additional analysis that only included thyroid cases as defined by receipt of treatment in AHS spouses, reported no evidence of a positive association between dicamba exposure and hypothyroid disease (HR: 0.93; 95% CI: 0.72, 1.21 with n = 60 exposed cases, 1,320 unexposed cases), and a further analysis that only included thyroid cases which were validated according to the *stricter case definition standards* (ascertained via medical record data; confirmed via validation questionnaire; reported thyroid disease at least twice in follow-up surveys) similarly reported no evidence of a positive association for dicamba exposure and hypothyroid disease (HR: 0.98; 95% CI: 0.71, 1.37; with n = 37 exposed cases, 770 unexposed cases).

The study quality was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths included the prospective cohort design, and the extensive methods used to obtain exposure information for several pesticides including dicamba. Study limitations included potential selection bias and self-reported hypothyroid disease. Selection bias was likely if study subject participation in the follow-up phases was related to their disease status for hypothyroidism and since thyroid disease was self-reported in this study, it was likely some cases misclassified their thyroid disease status and subtype. Additional study details regarding frequency and duration of pesticide use for dicamba would have been useful but were not provided.

- In a separate study, Goldner et al. (2013) evaluated the potential association between hypothyroid disease and dicamba and other pesticides using data from the AHS prospective cohort. The study population included male commercial and private pesticide applicators enrolled in the AHS, living in North Carolina and Iowa. Thyroid disease status was self-reported during follow-up interviews during Phase II (1999 – 2003) and Phase III (2005 – 2010) of the study. While the study investigated three subgroups of thyroid disease (hypothyroidism, hyperthyroidism, and 'other' thyroid disease), results for dicamba exposure were only reported for hypothyroidism. Pesticide exposure was reported through two self-administered questionnaires at enrollment (1993 – 1997) and captured pesticide exposures that occurred prior to enrollment. Among the 22,246 AHS study participants, 461 hypothyroid cases were reported, and of these, 289 reported ever use of dicamba. Of the 21,327 non-cases (no thyroid disease) with complete data, 11,685 reported ever use of dicamba. Logistic regression was used to analyze the association between ever use of dicamba and the occurrence of thyroid disease, adjusting for BMI, age at enrollment, and education. Evidence of a slight positive association was reported between exposure to dicamba and hypothyroid disease male commercial and private pesticide applicators, based on ever/never use (OR = 1.37; 95% CI: 1.13, 1.66; with n = 289 exposed cases and n = 11,685 exposed non-cases).

  The study quality was ranked moderate based on the study quality criteria in the OPP Framework. The prospective cohort study design and the detailed pesticide exposure information were considered study strengths. Limitations included self-reported diagnosis of thyroid disease rather than clinical confirmation which may have led to some cases misclassifying their thyroid disease subtype. Authors were unable to analyze incident cases separately from prevalent cases due to the manner in which data were collected. And as such, it is difficult to discern the temporal ordering of exposure and outcomes.

- Shrestha et al. (2018c) evaluated the association between incident hypothyroid disease and exposures to pesticides including dicamba. The study population consisted of private pesticide applicators enrolled in the AHS, an ongoing, prospective cohort study. Hypothyroid disease status was ascertained through self-report during follow-up interviews during Phase II (1999 – 2003), Phase III (2005 – 2010) and Phase IV (2013 – 2016) of the study. Validation of self-reported cases of hypothyroid disease was carried out using medical record data or two validation questionnaires.

Pesticide exposure was reported through self-administered questionnaires at enrollment (1993 – 1997). The Cox proportional hazards model was used to calculate HRs for hypothyroid disease, adjusting for smoking, education, state, and sex. Covariates were selected *a priori* based on potential for causal relationship identified in prior literature. Among the total number of study participants (n = 34,879), 829 hypothyroid cases and 34,050 non-cases were reported among private pesticide applicators. Among the hypothyroid cases (n = 829), 455 reported exposure to dicamba, based on ever/never use. Evidence of a slight positive association was reported between dicamba exposure and hypothyroid disease among private applicators (HR: 1.27; 95% CI: 1.08, 1.50, p-value < 0.01). A further analysis investigating the association between intensity-weighted lifetime days of use of dicamba and hypothyroid disease among private applicators, was conducted with the following tertiles intensity-weighted lifetime days of use for dicamba used: > 0 - ≤ 572 days of use, > 572 - ≤ 2,184 days of use, and > 2,184 days of use. Evidence of a positive association was reported for the middle and high exposure categories (*> 572 - ≤ 2,184 days* – HR: 1.32; 95% CI: 1.07, 1.63; with n = 157 exposed cases, p-value = 0.01); *> 2,184 days* - HR: 1.29; 95% CI: 1.04, 1.59; with n = 144 exposed cases, p-value = 0.02) but no evidence of a significant positive association was reported in the low exposure category *(> 0 - ≤ 572 days* - HR: 1.24; 95% CI: 1.00, 1.54; with n = 146 exposed cases, p-value = 0.05), and no evidence of a significant exposure-response trend (p-trend = 0.10). Evidence of a positive association was reported between ever-use of dicamba and hypothyroidism when the analysis was adjusted for the correlated pesticide imazethapyr (Phi coefficient ≥ 0.40) (HR = 1.31; 95% CI: 1.10, 1.56; p-value < 0.01). A further analysis investigating the association between intensity-weighted lifetime days of use of dicamba and hypothyroid disease among private applicators, further adjusted for the correlated pesticide imazethapyr, was conducted using same tertiles as reported above. Evidence of a positive association was reported for all three exposure categories (1.27 < all HRs < 1.35; all 95% CIs encompassed the null value of 1.0; p-values < 0.05; p-trend = 0.10) and no evidence of a significant exposure-response trend.

Additional sub-analyses investigated the association between dicamba exposure and hypothyroidism (based on ever/never use) while placing various restrictions on the case definition and evidence of a positive association was reported for each of the following analyses: 1) hypothyroid cases that were further restricted to those taking thyroid-related medications only (n = 35,073) (HR = 1.36; 95% CI: 1.14, 1.62; with n = 424 exposed cases, p-value = 0.01); 2) hypothyroid cases when female applicators were excluded (n = 34,375) (HR = 1.26; 95% CI: 1.06, 1.49; with n = 444 exposed cases, p-value = 0.01); 3) ever use of dicamba and hypothyroidism risk using inverse probability of censoring weights (HR: 1.28; 95% CI: 1.08, 1.51 n = 453, p-value = 0.01). And, no evidence of a significant positive association was reported for the analysis where hypothyroid cases were restricted to those confirmed by a validation questionnaire or medical records or who reported having hypothyroid disease ≥ 2 times or more in surveys (n = 34,464) (HR = 1.28; 95% CI: 0.99, 1.66; with n = 197 exposed cases; p-value = 0.06).

The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Strengths including the prospective cohort study design and the extensive methods used to assess cumulative pesticide exposure. Study limitations included the potential risk of bias due to loss to follow-up, and the possibility of selection bias if study subject participation in the follow-up phases was related to their disease status for hypothyroidism.

- Lerro et al. (2018) investigated the association between pesticide exposure including dicamba and hypothyroidism using data from the Biomarkers of Exposure and Effect in Agriculture (BEEA) study, a subset of the AHS prospective cohort. The BEEA was conducted from June 2010 to September 2013 and cases included male pesticide applicators who were part of the AHS, lived in North Carolina or Iowa, and were ≥ 50 years of age at enrollment for BEEA with no previous diagnosis of

cancer (besides skin cancer). Eligible BEEA participants completed the AHS questionnaires at enrollment (1993 – 1997) and follow-up (1999 – 2003, 2005 – 2010), had no history of cancer, and no history of self-reported thyroid disease or thyroid medication use. Blood samples were collected by a trained phlebotomist and serum samples were measured to confirm subclinical hypothyroidism in each case, which the study reported as thyroid-stimulating hormone (TSH) levels > 4.5 mIU/L.[64] Pesticide exposure was assessed via the study questionnaires completed at enrollment and exposure data including frequency (average days/year) and duration (years) of use for individual pesticides including dicamba was obtained. Intensity-weighted lifetime days of use were calculated for each pesticide by multiplying lifetime exposure days by an intensity-weighted factor. A logistic regression was performed to determine ORs and 95% CIs for the association between dicamba and hypothyroidism, adjusting for age, smoking, state, BMI, and correlated pesticides. The following exposure categories for dicamba were used: 36 – 350 days, > 350 – 1,046 days, > 1,046 – 2,699 days, and > 2,699 – 107,823 days. No evidence of a significant positive association was reported at any of the four exposure levels relative to the non-exposed group for subclinical hypothyroidism (0.68 < OR < 1.06; all 95% CIs encompassed the null value of 1.0; with 15 – 21 cases per exposure category; with a p-trend = 0.62).

The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Strengths including the prospective study design, laboratory confirmation of subclinical hypothyroidism, and the cumulative pesticide exposure assessment. The analysis was limited to cumulative pesticide use prior to enrollment and may have led to exposure misclassification.

EPA Conclusion

Overall, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and hypothyroid disease. Five publications (Goldner et al., 2010; Goldner et al., 2013; Shrestha et al., 2018b; Shrestha et al., 2018c; Lerro et al., 2018) examined the relationship between dicamba exposure and hypothyroid disease among AHS study participants and the evidence is mixed. For female spouses of male pesticide applicators enrolled in the AHS, Goldner et al. (2010) reported no evidence of a positive association between dicamba ever use and hypothyroid disease. The publication was ranked low due to a cross-sectional study design since temporality for exposure in relation to the outcome could not be determined and was limited by self-reported outcome. Shrestha et al. (2018b) reported no evidence of a significant positive association among female spouses of pesticide applicators in the AHS, based on dicamba ever use and longer follow-up time and was ranked moderate quality. Study limitations included self-reported diagnosis of thyroid disease and selection bias if study subject participation was related to their outcome.

Among male pesticide applicators in the AHS, five studies investigated the association between dicamba exposure and hypothyroid disease and reported mixed findings. Goldner et al. (2013) reported evidence of a slight positive association between exposure to dicamba and hypothyroid disease based on ever use and was ranked moderate quality due to the self-reported diagnosis of thyroid disease. A fourth publication (Shrestha et al., 2018c) reported evidence of a slight positive association between dicamba exposure and hypothyroid disease among private pesticide applicators enrolled in the AHS and included additional follow-up time to Goldner et al. (2013). Additionally, Shrestha et al. (2018c) reported evidence of a positive association for the middle and high, but not the low, exposure categories in the exposure-response analysis, but no evidence of a significant exposure-response trend. However, in an additional

[64] LeFevre ML; U.S. Preventive Services Task Force. Screening for thyroid dysfunction: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2015; 162:641–50.

analysis that restricted cases to those that were confirmed either through a validation questionnaire completed by the participant, medical records, or by the participant reporting having hypothyroid disease ≥ 2 times on surveys, the no evidence of a significant positive association was reported. The study quality was ranked moderate and study limitations were noted including the self-reported diagnosis of thyroid disease and the possibility of selection bias if study subject participation in the follow-up phases was related to their disease status for hypothyroidism. Finally, a fifth publication, (Lerro et al. 2018), reported no evidence of a significant positive association at any exposure level relative to the non-exposed group for subclinical hypothyroidism among male participants in the AHS.

Other Thyroid disease

One study (Goldner et al., 2010) evaluated the potential relationship between dicamba exposure and other thyroid disease in women.

Goldner et al. (2010) evaluated the association between prevalent thyroid disease and dicamba and other pesticides among female spouses of male private applicators in a cross-sectional analysis of data from the AHS prospective cohort. The study population included all female spouses of male private applicators who completed both the enrollment questionnaire on pesticide exposure (1993 – 1997) and the follow-up telephone interview collecting information on history of thyroid disease (1999 – 2003) and had complete data on all covariates. Cases of physician-diagnosed thyroid disease were ascertained through self-report during follow-up interviews (1999 – 2003) and were further classified into three subgroups: hypothyroidism, hyperthyroidism, and other thyroid disease. Pesticide exposure among female spouses of male private applicators was reported through the Spouse Enrollment Questionnaire given at enrollment (1993 – 1997) and included direct pesticide exposure (ever use of dicamba), but not indirect pesticide exposure of the spouse (husband's use of the pesticide). Polytomous logistic regression was used to analyze the association between ever use of dicamba and the occurrence of thyroid disease, adjusting for BMI, age at enrollment, smoking status, hormone replacement therapy (ever/never), and education. Among the 2,043 total cases of thyroid disease reported among female spouses, 17 (4.6%) hyperthyroid cases, 27 (2.4%) hypothyroid cases, and 19 (3.4%) 'other' thyroid cases reported ever use of dicamba. No evidence of a positive association was reported for the association between dicamba exposure and other thyroid disease (OR = 0.96; 95% CI: 0.60, 1.50; with n = 19 exposed cases).

The study quality was ranked low based on the study quality criteria provided in the OPP Framework. Authors were not able to analyze incident cases separately from prevalent cases due to the way the data were collected. The cross-sectional study design was a limitation since temporality for exposure in relation to the outcome could not be determined. Reliance on self-report of the outcome without clinical confirmation was another limitation. Additionally, the investigators were only able to assess ever/never exposure and did not have more detailed exposure information to assess cumulative dicamba exposure.

EPA Conclusion

Overall, there is *no epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and other thyroid disease. One publication (Goldner et al., 2010) examined the relationship between dicamba exposure and other thyroid disease among female spouses of private pesticide applicators enrolled in the AHS. Goldner et al. (2010) reported no evidence of a positive association between dicamba ever use and other thyroid disease among female spouses of pesticide applicators enrolled in the AHS. The publication was ranked low due to a cross-sectional study design since temporality for exposure in relation to the outcome could not be determined and the study was also limited by self-reported outcome.

3.7 Epidemiology Conclusion

OPP performed a systematic review of the epidemiologic literature on dicamba exposure and identified 78 peer-reviewed publications that investigated dicamba exposure and a range of adverse health outcomes, including 33 studies on carcinogenic health outcomes and 45 on the non-carcinogenic health outcomes affecting several organs, as well as autoimmune disease, Parkinson's disease, myocardial infarction, respiratory effects and birth effects and birthweight in children. OPP's conclusions on the available evidence for these outcomes are summarized below.

3.7.1 Carcinogenic Health Outcomes

Twenty-seven cancer outcomes were examined in 33 epidemiologic studies, with most cancer outcomes investigated in one or two studies. OPP concluded there was *no epidemiological evidence* of a clear associative or causal relationship between dicamba exposure and six cancer outcomes: colorectal cancer, rectal cancer, cancer of the larynx, stomach cancer, testicular cancer, and tongue cancer. This conclusion was based on evidence that was limited to studies on each cancer outcome that reported no evidence of a positive association between dicamba exposure and the cancer outcome (e.g., all reported OR effect estimates were ≤ 1.0).

OPP concluded there was *insufficient epidemiological evidence* of a clear associative or causal relationship between dicamba exposure and twenty-one cancer outcomes: cancers (all combined), bladder cancer, brain and spinal cancer (glioma), breast cancer, colon cancer, esophageal cancer, lip cancer, liver and intrahepatic bile duct cancer, lung cancer, hematopoietic cancer, leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, mantle cell lymphoma, multiple myeloma, melanoma, pancreatic cancer, prostate cancer, cancer of the small intestine, soft tissue sarcoma, tonsil cancer. The majority of these cancer outcomes were also only investigated in a single study population, with cancer (all sites), bladder cancer, and brain and spinal cancers, and leukemia all investigated in 3 studies, lung cancer and Hodgkin lymphoma in four studies each, multiple myeloma in five, and NHL and prostate cancer examined in nine studies each. Given the limited number of studies available for each outcome other than NHL and prostate cancer, there was minimal confidence in the available evidence so additional epidemiological evidence could substantively affect the overall magnitude or direction of any observed associations. Further information on the evidence for each health is summarized below.

- For all cancers, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and all cancers. This determination was based on three studies, (Flower et al., 2004; Samanic et al., 2006; Lerro et al., 2015). Flower et al. (2004) reported no evidence of a positive association between prenatal dicamba exposure and childhood cancer (all cancers combined) in the AHS prospective cohort. The overall quality of the study was moderate as the study relied on ever/never exposure assessment. Samanic et al. (2006) and Lerro et al. (2020) with longer follow-up time and more cases reported no evidence of a significant positive association between dicamba intensity-weighted lifetime days of use and all cancers combined among adults in the AHS prospective cohort. Both studies were ranked moderate as they did not adjust statistically for multiple comparisons.

- For bladder cancer, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and bladder cancer. This determination was based on three studies (Samanic et al., 2006; and Koutros et al., 2016; Lerro et al., 2020), that investigated the potential association between dicamba exposure and bladder cancer among the AHS prospective cohort each with increasing follow-up time and number of cases. Samanic et al. (2006), with follow-up through 2002, reported evidence of a positive association in the

middle exposure category of intensity-weighted lifetime days of dicamba use with the low exposure group as the referent among a very small number of cases. And, no evidence of a significant positive association between dicamba exposure and bladder cancer in any exposure category of intensity-weighted lifetime exposure days and lifetime exposure days with the no exposed group. Koutros et al. (2016), with follow-up through 2011, reported no evidence of a positive association between dicamba exposure and bladder cancer among AHS pesticide applicators based on ever/never use and no evidence of a significant positive association between intensity-weighted lifetime days of dicamba exposure and bladder cancer. The quality of the study was ranked high. And the third study, Lerro et al. (2020), with follow-up through 2015, reported no evidence of a significant positive association based on intensity-weighted lifetime days of dicamba exposure and bladder cancer. Both Samanic et al. (2006) and Lerro et al. (2020) were ranked moderate study quality and multiple comparisons without adjustment for multiple comparisons was considered a limitation.

- For brain and spinal cancer (glioma), there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and brain and spinal cancer. This determination was based on three studies (Lee et al., 2005, Yiin et al., 2012; Lerro et al., 2020) that investigated the relationship between dicamba exposure and brain and spinal cancers among three separate populations in the United States. Lee et al. (2005) reported no evidence of a significant positive association between dicamba ever use and glioma among farmers in Nebraska and among those cases who had a proxy respondent using a case-control analysis. The study was ranked low quality due to the large proportion of proxy respondents, reference group to nonfarmers, ever use assessment rather than exposure-response, and self-report of exposure. Yinn et al. (2012), in a case-control analysis among participants of the Upper Midwest Health Study, reported no evidence of a positive association between dicamba ever use and glioma and again when proxy respondents were excluded. The quality of the study was ranked moderate due to the large proportion of proxy respondents, self-report of exposure, and case-control study design. A third publication, Lerro et al. (2020), reported no evidence of a significant positive association between intensity-weighted lifetime days of dicamba and brain cancer among pesticide applicators in the AHS among a small number of cases. The overall quality of the study was ranked moderate and authors did not correct for multiple comparisons.

- For breast cancer, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and breast cancer. This determination was based on one publication (Engel et al., 2005) that examined the association between dicamba exposure and breast cancer among female spouses of pesticide applicators in the AHS prospective cohort and reported no evidence of a significant positive association for either direct dicamba exposure or indirect exposure (measured through husband's ever use of dicamba) and breast cancer. The overall quality moderate and limitations included the potential for exposure misclassification from self-reported previous pesticide exposures by study participants, and the indirect exposure assessment based on husband's pesticide use.

- For colon cancer, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and colon cancer. This determination was based on three publications (Samanic et al., 2006; Lee et al., 2007; Lerro et al., 2020) that examined the association between dicamba exposure and colon cancer among the AHS prospective cohort pesticide applicators. Lee et al. (2007) reported no evidence of a positive association between dicamba exposure and colon cancer among the AHS particpants, based on ever use of dicamba and was ranked high quality. Samanic et al. (2006) and Lerro et al. (2020) with longer follow-up time, both reported no evidence of a significant positive association between intensity-weighted lifetime days of dicamba exposure and colon cancer an no evidence of an exposure-

response trend. The study quality of both studies was ranked moderate. Strengths of the studies included the ascertainment of colon cancer and the exposure assessment, the primary limitation of both studies was the multiple comparisons without statistical correction of multiple comparisons, which likely resulted in incorrectly concluding significant associations.

- For esophageal cancer, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and esophageal cancer. This determination was based on two publications (Lee et al., 2004; Lerro et al., 2020) that examined the association between dicamba exposure and esophageal cancer. Lee et al. (2004) reported no evidence of a positive association among the participants of the Nebraska Health Study II in a case-control study of adults in Nebraska. The study was low quality due to several limitations including the study design, control selection, and comparison of farmers to nonfarmers, and the large number of proxy respondents. Lerro et al. (2020) reported evidence of a positive association in the third exposure category of intensity-weighted lifetime days of exposure and no evidence of a positive association in the first, second, and fourth exposure categories and no evidence of an exposure-response trend among the AHS cohort. The study was moderate quality and while the outcome and exposure assessments were strong, a notable limitation was the multiple comparisons without statistical correction.

- For lip cancer, *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and lip cancer. One study, Lerro et al. (2020) reported no evidence of significant positive association between intensity-weighted lifetime days of dicamba exposure and lip cancer among pesticide applicators in the AHS. Lerro et al. (2020) had several strengths including its prospective design, the ascertainment of colon cancer, and the exposure assessment, but the primary limitation was the multiple comparisons without statistical correction of multiple comparisons, which likely resulted in incorrectly concluding significant associations.

- For liver and intrahepatic bile duct cancer, *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and liver and intrahepatic bile duct cancer. One study, Lerro et al. (2020), reported evidence of a positive association between intensity-weighted lifetime days of exposure among a very small number of cases (n = 10 cases) at the highest exposure level > 3,689.0 days of exposure. No evidence of a significant positive association was reported for the two middle exposure categories among a very small number of cases (n = 6 – 8) and evidence of a significant inverse association was reported for the lowest exposure category (5.0 - 449.5 days) among a very small number of cases (n = 4). Additionally, when considered separately, Lerro et al. (2020) reported evidence of a moderately strong positive association in the high exposure group (> 1,260 days) of intensity-weighted lifetime exposure days and liver cancer and a significant exposure-response trend among a very small number of cases (n = 5). While Lerro et al. (2020) reported evidence of a positive association between dicamba and liver and intrahepatic bile duct cancers, the overall evidence was considered insufficient because there was only a single study available. It should be noted that while the overall study population was large, the study may have limited ability to fully evaluate the relationships between dicamba and liver and intrahepatic bile duct cancers because of the relatively small number of exposed cases (i.e., < 10 exposed cases) per exposure quartile. Additionally, this is a first time finding for the AHS study population and authors typically require repeated findings over additional studies. Finally, authors performed multiple comparisons without statistical correction, which likely resulted in incorrectly concluding significant associations.

- For lung cancer, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and lung cancer. This determination was based on four available publications (Alavanja et al., 2004; Samanic et al., 2006; Bonner et al., 2017; Lerro et al., 2020) that used data from the AHS prospective cohort to examine the association among male pesticide applicators. The first study, Alavanja et al. (2004) reported evidence of a strong positive association between dicamba exposure and lung cancer at the highest exposure level, among a very small number of cases (n = 8) and with the low exposed group as the referent. No evidence of a significant positive association was reported for any other exposure category with the low exposure group as the referent and for any exposure category with the no exposed group as the referent. Alavanja et al. (2004) was ranked high quality. Samanic et al. (2006) and Bonner et al. (2017) each reported no evidence of a significant positive association between dicamba exposure and lung cancer for either lifetime or intensity-weighted days of exposure. And the fourth study, with the longest follow-up time and largest number of cases, reported no evidence of a positive association between dicamba intensity-weighted lifetime days and lung cancer. The quality of the three studies was moderate and limitations included the high percentage of missing data the multiple comparisons without adjustment and potential issues with confounding.

- For hematopoietic cancers, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and hematopoietic cancers. This determination was based on one study (Samanic et al., 2006) that investigated the relationship between dicamba exposure and hematopoietic cancers among pesticide applicators in the AHS prospective cohort and reported no evidence of a significant positive association, based on intensity-weighted lifetime days of use. The study quality was moderate and several tests were performed without correcting for multiple comparisons, which likely resulted in incorrectly concluding significant associations.

- For leukemia, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and leukemia. This determination was based on three publications (Brown et al., 1990; Metayer et al., 2013; Lerro et al., 2020) that examined the association in adults and in children. Brown et al. (1990) assessed the association between dicamba exposure and leukemia among farmers living in Iowa and Minnesota by conducting a population-based case-control study. No evidence of a positive association was reported, based on ever/never use. The study quality was ranked moderate and limitations included recall bias and the use of proxy respondents among the cases and controls which both likely led to exposure misclassification. We also noted that the observed number of cases exposed to dicamba was small (10 < exposed cases < 20). Metayer et al. (2013), evaluated the association between childhood acute lymphoblastic leukemia (ALL) and pesticide exposure within the home in California using a population-based case-control study and reported no evidence of a positive association among children. The quality of the study was ranked moderate. Limitations included the indirect measurement of dicamba exposure through dust samples in the home which may be a poor surrogate for pesticide exposure (children likely spend several hours of the day out of the house at school) and exposure measurement occurred at a single timepoint approximately 1-2 years after diagnosis. And, a third publication, Lerro et al. (2020), reported no evidence of a significant positive association for any exposure category for cumulative intensity-weighted days of dicamba exposure for all leukemias combined among adults. Among subtypes, a associations were reported between dicamba exposure and acute myeloid leukemia at the middle exposure category, and at the low and high exposure levels and a significant exposure-response trend for acute/other lymphocytic leukemia among a very small number of cases. Over fourty statistical tests were performed between dicamba and cancer outcomes, without correction for the multiple comparisons. We would expect several of the significant findings to no longer be significant after statistical correction. We also note that the number of exposed cases

was very small for several exposure categories which severely restricts our ability to interpret with confidence the observed risk ratios as well as the ability to assess the exposure-response relationship.

- For Hodgkin Lymphoma (HL), there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and HL. This determination was based on four studies (Pahwa et al., 2006; Karunanayake et al. 2012; Latifovic et al., 2020; Lerro et al., 2020) that examined this association among three study populations, the Cross-Canada Study of Pesticides and Health Study (CCSPH), the North American Pooled Project (NAPP) in Canada and the United States, and the Agricultural Health Study (AHS) populations. All four publications reported no evidence of a significant positive association between dicamba and HL in a and all four studies were moderate quality. Study limitations consisted of the potential for selection bias, recall bias, low response rate, different selection methods used for cases and controls, and different exposure assessments across studies. Additional limitations noted in Lerro et al. (2020) were the multiple comparisons between dicamba exposure and several cancers and no adjustments for multiple comparisons were made. HED would expect several of the statistically significant results would no longer remain significant after appropriate adjustments that would account for the multiple comparisons performed. Too, HED notes several concerns with respect to confounder adjustments that suggest there may be issues with sample size and/or the statistical model/statistical analysis that may affect the reliability of the analysis.

- For non-Hodgkin's Lymphoma (NHL), there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and NHL among men. This determination was based on nine available publications (Cantor et al., 1992; McDuffie et al., 2001; McDuffie et al., 2005; De Roos et al., 2003; Hartge et al., 2005; Samanic et al., 2006; Czarnota et al., 2015; Leon et al., 2019; Lerro et al., 2020) that examined dicamba exposure and NHL. Eight studies reported no evidence of a significant positive association between dicamba exposure and NHL and the ninth study reported no evidence of a positive association. All studies were moderate quality and limitations included potential recall bias due to the cases remembering exposure differently than controls, different selection methods for cases and controls across studies, different methods for capturing pesticide exposure information (list of pesticides vs. voluntary recall), and use of a large number of proxy respondents.

- For the NHL subtypes, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and any NHL subtype.

    - For *mantle cell lymphoma*, Lerro et al. (2020) reported evidence of a strong positive association between intensity-weighted lifetime days of dicamba exposure and *mantle cell lymphoma* at both the low and high exposure levels, and no evidence of an exposure response trend among a very small (<10) number of exposed cases.

    - For *chronic/small lymphocytic leukemia*, Lerro et al. (2020) reported evidence of a significant negative association in the lowest exposure category among a small number of cases and no evidence of a significant positive association was reported for any exposure category of cumulative intensity-weighted days of dicamba exposure and *chronic/small lymphocytic leukemia.* While Lerro et al. (2020) had several strengths including the prospective study design, use of cancer registries to ascertain cases, and a validated questionnaire to assess pesticide exposure, several limitations were noted. In particular, over 40 different cancer analyses were performed and no adjustments for multiple comparisons were made. Several of the statistically significant results would no longer remain significant after appropriate

adjustments that would account for the multiple comparisons performed. Additionally, with respect to confounder adjustments, we note several concerns that suggest there may be issues with sample size and/or the statistical model/statistical analysis that may affect the reliability of the analysis. Further, the reported association between dicamba exposure and mantle cell lymphoma is a first time (exploratory) finding and AHS practice is to require a second follow-on confirmatory finding to begin to consider making any conclusions.

- For the NHL subtype, *multiple myeloma (MM)*, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and MM. This determination was based on five publications (Brown et al., 1993; Pahwa et al., 2006; Pahwa et al., 2012; Leon et al., 2019; Lerro et al., 2020). All five studies reported no evidence of a significant positive association between dicamba exposure and MM. The three case-control studies and the cohort study on the AHS were all moderate quality and study limitations included exposure misclassification, comparison of farmers to non-farmers, selection bias, recall bias, and multiple comparisons without statistical correction. The fifth study, Leon et al. (2019), was low quality, limitations included exposure misclassification, methods used to measure covariates, and incomplete adjustment for important potential confounders.

- For melanoma, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and melanoma. This determination was based on two publications (Samanic et al., 2006; Lerro et al., 2020) that examined the relationship between dicamba exposure and melanoma among the AHS prospective cohort population. Both publications reported no evidence of a significant positive association between dicamba exposure and melanoma and the study quality for both studies was moderate. Study limitations noted included the multiple comparisons without statistical correction in both studies.

- For pancreatic cancer, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and pancreatic cancer. This determination was based on two AHS studies (Andreotti et al., 2009; Lerro et al., 2020) that reported no evidence of significant positive association between intensity-weighted lifetime days of dicamba use and pancreatic cancer. Both studies benefited from the general strengths of the AHS including the exposure assessment, and outcome ascertainment via state cancer registries. Andreotti et al. (2009) was high quality and Lerro et al. (2020) was moderate quality with the noted limitation of multiple comparisons without statistical correction.

- For prostate cancer, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and prostate cancer. This determination was based on nine studies (Alavanja et al., 2003; Samanic et al., 2006; Band et al., 2011; Barry et al., 2011; Barry et al., 2012; Koutros et al., 2011; Christensen et al., 2016; Koutros et al., 2013; Lerro et al., 2020) that examined the association among the AHS prospective cohort and in a population-based case-control study among farm workers in British Columbia, Canada. All eight of the AHS studies reported no evidence of a significant positive association between dicamba exposure and prostate cancer. The study quality for all eight studies was either high or moderate and all benefited from the general strengths of the AHS including the prospective study design (three were nested-case control), and linkage to cancer registries to ascertain cases. Study limitations were noted, namely potential for exposure misclassification and missing data among cases (~30% of the cases) and multiple comparisons without adjustment for multiple comparisons. The ninth publication, Band et al. (2011), evaluated the association between dicamba and prostate cancer in a population-based

case-control study among farm workers in British Columbia, Canada and reported evidence of a moderately strong positive association in the high exposure category of the exposure-response analysis among a very small number of cases (n = 8). The study was moderate quality and limitations included selection bias and recall bias due to proxy respondents inaccurate recall of exposure. We note also, the number of dicamba-exposed prostate cancer cases in the high exposure category (n = 8) was very small.

For cancer of the small intestine, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and cancer of the small intestines. This determination was based one study, Lerro et al. (2020) that examined the association among the AHS prospective cohort and reported no evidence of a significant positive association in any exposure category of intensity-weighted lifetime days of exposure. The study was moderate quality and while the study had several strengths including the prospective study design, use of cancer registries to ascertain cases, and a validated questionnaire to assess pesticide exposure, several limitations were noted. In particular, over 40 different cancer analyses were performed and no adjustments for multiple comparisons were made and noted issues with confounder adjustments that suggest there may be issues with sample size and/or the statistical model/statistical analysis that may affect the reliability of the analysis.

- For soft tissue sarcoma (STS), there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and STS. This determination is based on two publications (Pahwa et al., 2006; Pahwa et al., 2011) that investigated the potential association between exposure to dicamba STS, in case-control analysis of participants of the Cross-Canada Study of Pesticides and Health Study while considering exposure to DEET (Pahwa et al., 2006) and medical and familial history of cancer (Pahwa et al., 2011). Both studies reported no evidence of a significant positive association between dicamba exposure and STS based on ever exposure and were moderate quality. Limitations included potential recall bias, as the cases living with the outcome may have remembered certain past exposures more accurately than the controls and the low response rate to the mailed questionnaire.

- For tonsil cancer, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and tonsil cancer. One study (Lerro et al., 2020) examined the association between dicamba exposure and tonsil cancer among the AHS prospective cohort and reported evidence of a positive association in the low exposure category and no evidence of a positive association in the high exposure category. Additionally, evidence of a significant exposure-response trend (p-trend < 0.001) was reported, with the no exposure group as the referent. This finding was reported among a small number of dicamba-exposed cases (n = 11). The study was moderate, and limitations included the multiple comparisons without statistical correction, confounder adjustments that suggest there may be issues with samples size and/or the statistical model/statistical analysis, and a first time finding that replication of future studies.

3.7.2 Noncarcinogenic Health Outcomes

Non-carcinogenic health outcomes were examined in 45 epidemiologic studies on 26 different adverse health outcomes. OPP concluded there was *no epidemiological evidence* of a clear associative or causal relationship between dicamba exposure and the outcomes: rheumatoid arthritis, depression, dream enacting behavior, monoclonal gammopathy of undetermined significance, sleep apnea, stroke, suicide, and other thyroid disease. This conclusion was based on evidence that was limited to a one or two studies on each health outcome that reported no evidence of a positive association between dicamba exposure and the health outcome of interest (e.g., reported OR effect estimates were ≤ 1.0).

OPP concluded there was *insufficient epidemiological evidence* of a clear associative or causal relationship between dicamba exposure and the remaining health effects: allergies, amyotrophic lateral sclerosis (ALS), autoimmune disease (antinuclear antibodies), birth defects, birthweight, diabetes, end stage renal disease, eye disorders, fatal injury, myocardial infarction (MI), olfactory impairment, Parkinson's disease (PD), respiratory effects (asthma, chronic bronchitis, rhinitis, wheeze), hyperthyroid disease, and hypothyroid disease. The majority of these effects were also only investigated in a single study population, and frequently reported no evidence of a significant positive association (e.g., OR > 1.00 but not significant). Given the limited number of studies available for each outcome, there was generally minimal confidence in the available evidence, so additional epidemiological evidence could substantively affect the overall magnitude or direction of any observed associations. Further information on the evidence for each health is summarized below.

- For allergies, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and allergy. One study (Weselak et al., 2007) examined the association between dicamba exposure during pregnancy and allergy among offspring among the participants Ontario, Canada, and reported no evidence of a significant positive association between dicamba exposure during pregnancy and allergy or hayfever in offspring, among a small number of cases. The study was ranked moderate quality and limitations included the potential for recall bias, exposure misclassification, and outcome misclassification. We also note the small number of dicamba exposed cases.

- For amyotrophic lateral sclerosis (ALS), there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and ALS. This determination was made based on one study (Kamel et al., 2012) that reported no evidence of a significant positive association, among a small number of cases. The quality of the study was ranked high and strengths included the prospective cohort study design, case ascertainment, and exposure assessment.

- For antinuclear antibodies- a marker of autoimmune disease, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and autoimmune disease. This determination was based on one study, Parks et al. (2019), that examined the association between dicamba exposure and risk of autoimmune disease among a subset of the AHS prospective cohort population enrolled in the Biomarkers of Exposure and Effect in Agriculture sub-cohort. Parks et al. (2019) reported no evidence of a significant positive association between dicamba exposure and biomarkers for autoimmune disease. The quality of the study was ranked moderate and benefited from the general strengths of the AHS, including the prospective cohort study design and the exposure assessment approach which examined cumulative lifetime exposure to dicamba. The study relied on self-reported doctor diagnosis of autoimmune disease at enrollment which was a study limitation, rather than clinical or medical record confirmation.

- For birth defects, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and birth defects and spontaneous abortion. This determination was based off of four publications (Arbuckle et al., 2001; Meyer et al., 2006; Weselak et al., 2008; Yang et al., 2014) that examined the association between dicamba exposure and birth defects. Two publications (Arbuckle et al., 2001; Weselak et al., 2008) utilized the Ontario Farm Family Health Study (OFFHS), a population-based retrospective cohort study conducted in Canada, to evaluate the effect of dicamba on spontaneous abortion and birth defects and reported no evidence of a significant positive association between dicamba exposure and spontaneous

abortion and preconception dicamba exposure and birth defects, among a small number of cases (Weselak et al., 2008). When stratified by gender, evidence of a moderately strong positive association was reported between preconception dicamba exposure and birth defects in male offspring, among a very small number of exposed cases. Both studies were ranked moderate quality and both had limitations including the potential for recall bias, exposure misclassification, and outcome misclassification. The third (Meyer et al., 2006) and fourth studies (Yang et al., 2014) used birth registries and maternal residence to geospatially assign prenatal dicamba exposure to assess the association between dicamba exposure and hypospadias and neural tube defects and orofacial clefts. Meyer et al. (2006) reported no evidence of a positive association between prenatal dicamba exposure and hypospadias in male offspring in Arkansas. Yang et al. (2014) used California registry data on birth defects and healthy births to identify cases and controls and CA PUR to ascertain exposure to dicamba and reported no evidence of a significant positive association between dicamba exposure based on maternal residence at birth and cleft palate in offspring. As such, both studies had similar strengths, but had substantive limitations in their exposure assessment because it is unclear if living within a certain distance (500m or 1,000 m) of agriculture land is a reliable indicator of maternal exposure to dicamba. Furthermore, we note the very small number of exposed cleft palate cases which severely restricts the ability to interpret with confidence the observed odds ratios.

- For birthweight, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between maternal dicamba exposure and birthweight in children. This determination was based on one AHS study, Sathyanarayana et al. (2010), that reported no evidence of a significant association between mother's ever use of dicamba and offspring's birthweight. The study quality was ranked low due to the cross-sectional study design since temporality for exposure in relation to the outcome could not be determined.

- For diabetes, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and diabetes. This determination was based on two available studies (Montgomery et al., 2008; Starling et al., 2014). Montgomery et al. (2008) reported no evidence of a positive association between ever use of dicamba and diabetes among AHS pesticide applicators and Starling et al. (2014) reported no evidence of a significant positive association among wives of pesticide applicators. Both studies were ranked moderate quality and study limitations included self-reported diagnosis of diabetes, the inability to control for diet and exercise, and possible selection bias in Montgomery et al. (2008) since a large number of participants who did not complete a follow-up questionnaire might have been diabetic at study enrollment.

- For end-stage renal disease (ESRD), there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and ESRD. This determination was based on two available publications (Lebov et al., 2015; Lebov et al. 2016). Lebov et al. (2015) evaluated the association between dicamba exposure and ESRD among the wives of pesticide applicators enrolled in the AHS. No evidence of a significant positive association was reported between indirect dicamba exposure and ESRD based on ever/never use, and no evidence of an exposure-response trend was observed. The overall quality of the study was ranked moderate. Study limitations included the indirect assessment of pesticide exposure for applicator wives using husband's use information as a surrogate. This approach has not been validated and may not be a reliable proxy for direct dicamba exposure by female spouses. Lebov et al. (2016) directly assessed dicamba exposure and ESRD among male pesticide applicators and reported no evidence of a significant positive association based on intensity-weighted lifetime days of exposure, with the no exposure group as the referent. The overall quality of the study was ranked high.

- For eye disorders, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba and eye disorders including age-related macular degeneration (AMD). This determination was based on two available studies (Kirrane et al., 2005; Montgomery et al., 2017) that examined eye disorders among the participants of the AHS cohort. Kirrane et al. (2005) reported no evidence of a significant positive association between dicamba exposure and retinal degeneration among wives of farmers in a cross-sectional analysis and was ranked low quality. In an update to Kirrane et al. (2005) that included longer follow-up time, Montgomery et al. (2017) reported evidence of a positive association in the highest exposure category of cumulative days of dicamba exposure and AMD, among a small number of cases. No evidence of a significant positive association was reported for any other exposure category. The study quality was ranked moderate.

- For fatal injury, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and fatal injury. This determination was based on one available study (Waggoner et al., 2013) that reported no evidence of a significant positive association between dicamba exposure and fatal injury among male pesticide applicators in the AHS. The study quality was ranked low. The prospective study design and collection of mortality data available through the National Death Index were study strengths; however, it is not clear if pesticide use at enrollment is a valid measure of exposure during the time interval that preceded fatal injury, as more pesticide use could be an indicator of use of more complex farm equipment which would increase risk of fatal injury.

- For myocardial infarction, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba and myocardial infarction (MI). This determination was based on two available publications on the AHS, Mills et al. (2009) and Dayton et al. (2010). Mills et al. (2009) examined the association between DDVP exposure and myocardial infarction (MI) among male pesticide applicators in the AHS, and reported no evidence of a significant positive association for either non-fatal MI and fatal MI and dicamba exposure, based on ever/never use. Dayton et al. (2010) reported no evidence of a positive association between dicamba exposure and MI among women in the AHS. The study quality of both studies was moderate. Study limitations included a limited amount of registry data available for non-fatal MI relative to fatal MI, and a shorter follow-up period for nonfatal MI relative to fatal MI. An additional limitation in the evaluation of non-fatal MI was that ascertainment relied on self-report and could have resulted in misclassification.

- For olfactory impairment, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and olfactory impairment. This determination was based on one available study, Shrestha et al. (2020a), that reported no evidence of a significant positive association between intensity-weighted lifetime days of dicamba exposure and olfactory impairment among pesticide applicators in the AHS. The quality of the study was moderate, and the self-reported outcome was a limitation.

- For Parkinson's disease (PD), there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and PD. This determination was based on two available studies (Kamel et al., 2007; Shrestha et al., 2020b). Kamel et al. (2007) reported no evidence of a significant positive association between dicamba exposure and incident Parkinson's disease among study participants enrolled in the AHS. The study quality was ranked moderate. Study limitations included recall bias, the lack of clinical confirmation of self-reported PD cases, and the diagnosis date and duration of pesticide use data was unknown for

prevalent PD cases. Shrestha et al. (2020b) further assessed cumulative, lifetime dicamba use among the AHS applicators and reported no evidence of a significant positive association between dicamba use and incident PD in the any exposure category of IWLD of dicamba use and no evidence of a significant exposure-response relationship.

- For respiratory effects (asthma, chronic bronchitis, rhinitis, and wheeze), there were eleven cross-sectional studies that included ten studies of the AHS cohort (Henneberger et al., 2014; Hoppin et al., 2002; Hoppin et al., 2006a; Hoppin et al., 2006b; Hoppin et al., 2007; Hoppin et al., 2008; Hoppin et al., 2009; Hoppin et al., 2017; Slager et al., 2010; Valcin et al., 2007) and one study of a Canadian cohort (Weselak et al., 2007). These studies generally reported no evidence of significant positive association for maneb/mancozeb and were limited in quality because they all relied on cross-sectional study designs and were unable to assess the temporal relationship between maneb/mancozeb exposure and respiratory effects.

  For the respiratory effect of asthma, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and asthma. This determination was based on four available publications (Weselak et al., 2007; Hoppin et al., 2008; Hoppin et al., 2009; Henneberger et al., 2014) that examined the association between dicamba exposure and asthma among the AHS population and the Ontario Farm Family Health Study population. Weselak et al. (2007) reported no evidence of a positive association between dicamba exposure during pregnancy and asthma in offspring in Ontario farm families. The study was moderate quality and was limited by the retrospective approach to gathering outcome and exposure information, potential for recall bias, and the self-reported outcome. The three additional studies examined the association between dicamba exposure and asthma in cross-sectional analysis among adults in the AHS cohort and reported no evidence of a significant positive association between dicamba ever use and men and women in the AHS. The quality of each of the three AHS studies was low due to the cross-sectional study design as temporality for exposure in relation to the outcome could not be determined. Additionally, the studies relied on self-report of the outcome.

- For the respiratory effect chronic bronchitis, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and chronic bronchitis. Three publications (Weselak et al., 2007; Hoppin et al., 2007; Valcin et al., 2007) examined the association between dicamba exposure and chronic bronchitis among Ontario farm families and the AHS prospective cohort population and reported no evidence of a significant positive association between dicamba exposure and chronic bronchitis among men and women in the AHS and among offspring (exposed through parents use during pregnancy) in Ontario. Weselak et al. (2007) was moderate quality and was limited by the retrospective approach to gather exposure and outcome information. The three AHS publications were low quality and used cross-sectional study designs to assess the association between dicamba and chronic bronchitis. As such, the studies were unable to assess the temporal association between dicamba exposure and chronic bronchitis. Additionally, studies failed to ask their study participants about respiratory signs and symptoms during enrollment. Since respiratory signs and symptoms are helpful in diagnosing chronic bronchitis, this medical information could have provided increased confidence in the diagnosis, potentially.

- For the respiratory effect, rhinitis, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and rhinitis. This determination was based on one available study (Slager et al., 2010) that examined dicamba exposure and rhinitis among private pesticide applicators and reported no evidence of a significant positive association based on ever use. The overall quality of the study was ranked low.

The cross-sectional study design was a main limitation since temporality for exposure in relation to the outcome could not be determined. Additionally, the study relied on self-report of the outcome.

- For wheeze, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and wheeze. This determination was based on four publications (Hoppin et al., 2002; Hoppin et al., 2006a; Hoppin et al., 2006b; Hoppin et al., 2017) that examined the association between dicamba exposure and wheeze among participants of the AHS prospective cohort. Hoppin et al. (2002), Hoppin et al. (2006a), and Hoppin et al. (2006b) reported no evidence of a significant positive association between dicamba exposure and wheeze among AHS pesticide applicators based on ever use of dicamba in the past year. Hoppin et al. (2017) reported evidence of a positive association between dicamba use in the past year and allergic wheeze and non-allergic wheeze, based on ever use. In the exposure-response analysis, evidence of a positive association was reported in the highest exposure category of allergic wheeze and in three of the four lowest exposure categories for nonallergic wheeze. The authors did not report a p-trend statistic for the exposure-response analysis for either allergic or non-allergic wheeze and dicamba; however, inspection of the ORs associated with each category suggests an exposure-response trend may not exist for either allergic or non-allergic wheeze. All four studies were ranked low quality, as they relied on a cross-sectional design that was unable to assess the temporality of the relationship between dicamba exposure and wheeze. Additionally, health outcomes were self-reported.

- For hyperthyroid disease, there is *no epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and hyperthyroid disease. This determination is based on three publications (Goldner et al., 2010. Shrestha et al., 2018b; Shrestha et al., 2019) that reported no evidence of a significant positive association among wives of pesticide applicators and pesticide applicators in the AHS population. Goldner et al. (2010) was cross-sectional in study design and as such, was unable to assess the temporal association between dicamba exposure and hyperthyroid disease and was ranked low quality. Shrestha et al. (2108b) and Shrestha et al. (2019) were both ranked moderate quality and were prospective in nature. However, both studies relied on self-reported hyperthyroidism even though the study authors attempted to clinically confirm some of the cases via medical record confirmation. Potential selection bias was also likely assuming study subject participation in the follow-up phases was related to their disease status for hyperthyroidism. An additional limitation of all three publications was that only ever use of pesticides prior to enrollment was captured rather than pesticide use that occurred after enrollment and this may have led to exposure misclassification.

- For hypothyroid disease, there is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between dicamba exposure and hypothyroid disease. This determination was based on five publications (Goldner et al., 2010; Goldner et al., 2013; Shrestha et al., 2018b; Shrestha et al., 2018c; Lerro et al., 2018) that examined the relationship between dicamba exposure and hypothyroid disease among AHS study participants and reported mixed results. Goldner et al. (2010) and Shrestha et al. (2018b) reported no evidence of a positive association between dicamba ever use and hypothyroid disease among female spouses of pesticide applicators enrolled in the AHS. Among male pesticide applicators in the AHS, Goldner et al. (2013) reported evidence of a slight positive association among male commercial and private pesticide applicators in the AHS, while Shrestha et al. (2018c) with longer follow-up time, reported evidence of a slight positive association between dicamba exposure and hypothyroid disease among private pesticide applicators enrolled in the AHS. Shrestha et al. (2018c) also reported evidence of a positive association in the middle and high exposure categories of intensity-weighted lifetime days of dicamba use and no evidence of an exposure-response trend among private applicators in the AHS. Although a prospective cohort study design was used in Goldner et al. (2013), the study was ranked moderate due

to the self-reported diagnosis of thyroid disease, and Goldner et al. (2010) was ranked low due to the cross-sectional study design as temporality for exposure in relation to outcome could not be determined. Shrestha et al. (2018b) and Shrestha et al. (2018c) were prospective cohort studies with longer follow-up time and were ranked moderate. Several limitations were noted including the self-reported hypothyroid disease and the possibility of selection bias if study participation in the follow-up phases was related to their disease status for hypothyroidism. The overall evidence for these outcomes, however, was considered insufficient because: (i) the available AHS studies had substantive limitations related to the assessment of only ever-never use of dicamba, (ii) self-report of hypothyroid disease; and (iii) there was no supporting information from other study populations to validate or corroborate the findings from the AHS cohort.

4 Overall Conclusion

For this Dicamba Tier II Incident and Epidemiology Report, HED found that overall, the majority of dicamba incidents were low in severity (84% in IDS, 86% in SENSOR-Pesticides, NPIC 69%). IDS, SENSOR-Pesticides and PISP identified that most incidents involved homeowners exposed either when applying the product or through spills/splashes of the product. Most often these exposures were to lawncare products with more than one active ingredient. In addition, postapplication exposure to non-applying members of the household following application were reported. Among the occupational exposures to dicamba, these too primarily involved exposures while applying the pesticide, several of these involved application equipment failures; secondly several agricultural workers were directly hit with the pesticide spray during an active pesticide application. Across all four incident databases reviewed, there was a total 29 of spray drift-related exposures. Dicamba cases often reported adverse dermal, respiratory, and gastrointestinal health effects. Many cases also reported adverse gastrointestinal and ocular health effects.

HED conducted a systematic review of the epidemiologic literature on dicamba in order to assess the epidemiologic evidence on the potential adverse effects of dicamba exposure, and identified 78 publications that investigated a range of health outcomes, including 33 studies on carcinogenic health outcomes and 45 on the non-carcinogenic outcomes. There were individual studies that identified positive association between dicamba and some adverse health effects, the overall evidence was based on a small body of studies (i.e., typically only one or two studies per health outcome) that often had substantive limitations with respect to their study design, exposure assessment approach, or outcome assessment. As such, HED concluded that overall, there was insufficient epidemiologic evidence to suggest a clear associative or causal relationship exists between dicamba exposure and the adverse health effects examined in the available epidemiologic literature. The Agency will continue to monitor the epidemiology data and – if a concern is triggered – additional analysis will be conducted.

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6 APPENDIX A: SUMMARY OF INCIDENTS REPORTED

Table 1. Single Ingredient Dicamba Incidents Reported to Main IDS from 2015 to July 31, 2020

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
028970 - 00001	6/22/2016	MO		NOT REPORTED	029801	No or unknown symptoms	Drift complaints involving the application of dicamba products cotton fields, soybean fields and a commercial tomato production field.
029268 - 00001	8/2/2016	NM	000100-00884	VANQUISH HERBICIDE	128931	Moderate	An adult male was driving his vehicle and was hit by the New Mexico Highway Department with product spray. Within a couple hours he developed blurry vision, upset stomach, and his skin felt odd. He went to the ER, they recommended showers and performed blood tests. The next day, he experienced nausea, blurry vision and muscle weakness.
030207 - 00031	6/28/2017	AL	000100-00884	VANQUISH HERBICIDE	128931	Moderate	An adult male who works with the product was exposed to the product twice. the first exposure, He was pouring the liquid concentrate and it splashed on his arms. He developed a severe reaction with a bad skin rash. He went to the ER and was treated with a steroid and antibiotics. His facility turns the product in to powder to make PVC covered polyester yarn. Two weeks later, he came into contact with the powder and developed a rash. He was not wearing PPE.
030490 - 00005	9/20/2017		000100-00884	VANQUISH HERBICIDE (PCP)	128931	Moderate	An adult female's yard was treated with the product by mistake. She has been experiencing pain in her nose, itchy skin, burning eyes, pain in her lungs, trembling, fatigue, breathing, difficulty, nausea, abdominal cramps, dizziness, and yellow secretions from her eyes, ear pain, sinus pain, throat pain. She has preexisting asthma.
030774 - 00002	1/12/2018			VANQUISH HERBICIDE	128931	Moderate	An adult male used the product spraying about 4000-5000 liter per day. At the time of exposure, he developed nausea, vomiting, coughing, muscle weakness and dizziness. Two years post exposure, he developed pulmonary issues.
031356 - 00001	7/8/2018	KS	000524-00617	XTENDIMAX WITH VAPORGRIP TECHNOLOGY	128931	Moderate	A 65 year old male was cutting weeds in a field. That night he developed a fever of 103. The next day he went to the ER and was diagnosed with sepsis. A farmer in another field across the road was spraying the product. There is no known direct contact with the mist. He also had a tick bite.

Table 1. Single Ingredient Dicamba Incidents Reported to Main IDS from 2015 to July 31, 2020

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
				FROM MONSANTO			
033142 - 00001	4/8/2020	OK	000524-00617	XTENDIMAX WITH VAPORGRIP TECHNOLOGY	128931	Moderate	A warehouse manager states that the product makes his employees noses bleed.

Table 2. Multiple AI Dicamba Death and Major Severity Incidents Reported to Main IDS from 2015 to July 31, 2020

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
030403 - 00011	8/7/2017	SMITHTOWN, NY	002217-00894-072155	ALL-IN-ONE LAWN WEED & CRABGRASS KILLER READY-TO-USE SPRAY	029802, 128974, 030019	Major	A senior (>64 years old) male sprayed the product. Within approximately 30 minutes, he began to develop eye irritation and lung irritation and was subsequently seen at the local ER. Following a medical evaluation, he was found do have blood clots in his lungs. The physicians do not think that his use of the product is related to the events.
030497 - 00002	9/15/2017	NEW YORK, NY	002217-00930	Q4 PLUS TURF HERBICIDE FOR GRASSY & BROADLEAF WEEDS	129081, 128974, 030019, 029802	Major	A 68 year old male applied the product over a three week period. He was admitted to the hospital with hives, itchiness, blurred vision, eye swelling and partial body paralysis. The physicians determined that his symptoms were related to his blood pressure medication and not the product.
032021 - 00002	3/25/2019	SAN ANTONIO, TX	009688-00342-008845	SPECTRACIDE WEED STOP FOR LAWNS CONCENTRATE 2	030019, 029802, 031520, 129081	Major	An adult male was exposed to the product when the hose adapter attached to the bottle blew off and the product got into his eyes. He experienced seeing spots and having trouble seeing.
032461 - 00023	7/3/2019	MOBILE, AL	009688-00337-008845	SPECTRACIDE WEED STOP FOR LAWNS PLUS CRABGRASS KILLER 3	129081, 128974, 030019, 029802	Major	46 year old male ingested 1/3 of a bottle of herbicide. He experienced drowsiness, hypersecretions and was intubated.

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Table 2. Multiple AI Dicamba Death and Major Severity Incidents Reported to Main IDS from 2015 to July 31, 2020

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
				And DIESEL FUEL (GENERAL FORMULATION)			
032461 - 00036	7/27/2019	SEATTLE, WA	009688-00109-008845	SPECTRACIDE WEED STOP FOR LAWNS and 30 SECONDS OUTDOOR CLEANER - CONCENTRATE	029802, 030019, 031520	Major	62 year old male has presented to ED and admitted with suspected organophosphate poisoning. He had been applying Spectracide Weed Stop For Lawns and was also using 30 Seconds Outdoor cleaner. He was found down by spouse later in evening. He presented with bad rash and blisters all over his body with increased oral secretions, lacrimation, watery yellow diarrhea and altered mental status requiring intubation. Self-harm was not expected.
032489 - 00001	9/4/2019	HERSHEY, PA	009688-00265-008845	SPECTRACIDE WEED & GRASS KILLER CONCENTRATE 2	122809, 029802, 032201	Death	Suicide - male ingested an entire bottle of the product.
032714 - 00013	11/29/2019	NEW CANEY, TX	000478-00121-008845	ELIMINATOR LAWN WEED KILLER READY-TO-SPRAY	030019, 031520, 029802	Major	An adult male sent a letter to the company stating that the product caused respiratory problems and that the product was harmful, fatal to breath, and that he developed severe respiratory problems.

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Moved down [2]: Table 3. Dicamba Incidents reported to Main IDS from 2019-July 31, 2020[65]

Table 3. Dicamba Incidents reported to Main IDS from 2019-July 31, 2020[66]

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
032149 - 00005	3/27/2019	FORT WORTH, TX	092564-00061	BIANOVA ADVANCED 3-IN-1 WEED & FEED FOR SOUTHERN LAWNS	080818, 119031, 029801	Moderate	Caller reports that he was using these products at his home about 8 days ago and thinks he may have gotten an exposure to some of the powder when the air was blowing. Caller says he did not have long sleeves so it's possible that the product could have gotten on him. Caller is really uncertain as he doesn't remember being exposed to the product but 5 days later, he began developing a rash, itching and red skin over 50% of his body including his arms and all of his back. Caller's wife came on the phone and explained that the itching was keeping him from sleeping at night, so they went, in, to an Urgent Care Clinic today to get some relief for him. The doctors were unsure what is causing the AE and had asked about anything new that they may be using. Caller reports that he has used the product in the past and he's never found himself to be allergic or sensitive to anything. The doctors aren't sure what is causing the reaction but have prescribed Kenalog Cream, Triamcinolone, Atarax and a Pyrethrin as they are also treating for a possible case of scabies.
033135 - 00001	12/25/2019	CA	092564-00043	BIOADVANCED SCIENCE-BASED SEASON LONG WEED CONTROL FOR LAWNS CONCENTRATE	129043, 125851, 119046, 030019	Minor	a 32 year old male intentionally ingested 24 oz of home use 2,4-D/Dicamba in an apparent self-harm attempt.
032441 - 00002	7/14/2019	LOS ANGELES, CA	092564-00042	BIOADVANCED ALL-IN-ONE LAWN WEED & CRABGRASS	030019, 128974, 029802	Moderate	39 year old female reports that she used the product to spray her backyard on 7/14/2019. She says she began spraying, and almost immediately, began to have a chemical taste in her mouth. She reports that her tongue

[66] Incident with an * are also listed in Table 2. Multiple AI Dicamba Death and Major Severity Incidents Reported to Main IDS from 2015 to July 31, 2020.

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Table 3. Dicamba Incidents reported to Main IDS from 2019-July 31, 2020[a]

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
				KILLER1 READY-TO-SPRAY			and lips were hurting and felt it was swelling, she felt tightness in her chest and was having shortness of breath, nasal, oral and respiratory irritation and excessive salivation. In addition, her hands were itching, and she says she was wearing gloves, so she has no idea how any product got onto her hands. She reports that she called Poison Control and they suggested that she'd been poisoned by something. They recommend that she go to the ER for an evaluation. Caller reports that the symptoms didn't improve but she had no way to go to the ER as she had a small child and there was no one to care for the child if she went to the hospital. She denies using any therapies or treatments during the next 4 days. She says her husband was out of town and was to return on 7/18/2019 so she waited. By that time, she was still having the same effects and she had, also, started having diarrhea. She reports that her mouth and lips were dry and painful, but her lips were, also, numb. Her lymph nodes seemed swollen and she was having muscle cramps. She reports that her speech continued to be slurred so when her husband arrived, caller went to her local ER and this was about 1:00 am. When she got there and explained her symptoms., they took her in, immediately, Caller says they did some unspecified blood work and a chest X-Ray. She was told that both results were good. She was told she has a chemical exposure and should follow up with and ENT and with her PCP. She was also told to get plenty of fresh air and to avoid chemicals, including any detergents. She reports that the doctors told her that they didn't think this was an allergic reaction but suggested she try taking some Benadryl to see if it would help. Caller says she came home and did try Benadryl with no improvement. She made an appt. for 7/23/2019 with an ENT specialist and has an appt. with her PCP on 7/25/2019. Caller feels she's been poisoned and says the product did not

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Table 3. Dicamba Incidents reported to Main IDS from 2019-July 31, 2020[x]

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							recommend or require the use of any protective gear or a mask.
033124 - 00002	2/27/2020	MOUNT DORA, FL	092564-00004	BIOADVANCED SOUTHERN WEED KILLER FOR LAWNS READY-TO-SPRAY	029802, 030019, 031520	Moderate	A 71 year old male sprayed the lawn using this product. He did not have gloves on and had canvas shoes with holes in them. A couple areas he overlapped, so his feet got wet. When he was done spraying, he went and took off his shoes and washed feet and hands with soap and water. Caller reports he still has symptoms on his right hand and bilateral feet. He describes his symptoms as dry, cracked, peeling skin that is dry underneath 'like a sunburn'. He has been applying honeybee lotion and gold bond with aloe to help soothe symptoms. He denies any blisters or open areas at this time.
032314 - 00021	6/4/2019	DAYTON, TX	034704-00869	RIFLE-D HERBICIDE	030019, 029802	Minor	A 27 year old male got sprayed in the face with the product. He washed his face with soap and water. He experienced a headache.
032277 - 00002	6/24/2019	FORT COLLINS, CO	010404-00043	LESCO THREE-WAY SELECTIVE HERBICIDE	031520, 029802, 030019	Minor	An adult female experienced eye irritation after her apartment complex was sprayed and the vapors came in through the window.
032277 - 00003	4/16/2019	TULSA, OK	010404-00043	LESCO THREE-WAY SELECTIVE HERBICIDE	030019, 029802, 031520	Minor	an adult male used the product and a small amount hit his lips. He washed his lips for 15 minutes. He experienced swollen lips.
032485 - 00001	7/2/2019	BETHESDA, MD	010404-00043	LESCO THREE-WAY SELECTIVE HERBICIDE	030019, 031520, 029802	No Effects	An adult female had skin exposure to the product.
033353 - 00004	4/2/2020	DURHAM, NC	010404-00043	LESCO THREE-WAY SELECTIVE HERBICIDE	031520, 030019, 029802	No Effects	An adult male was praying the product and some of it got on his face. He flushed his face with water. He did not report any symptoms.
032021 – 00002*	3/25/2019	SAN ANTONIO, TX	009688-00342-008845	SPECTRACIDE WEED STOP FOR LAWNS CONCENTRATE 2	030019, 029802, 031520, 129081	Major	An adult male was exposed to the product when the hose adapter attached to the bottle blew off and the product got into his eyes. He experienced seeing spots and having trouble seeing.
032461 – 00023*	7/3/2019	MOBILE, AL	009688-00337-008845	SPECTRACIDE WEED STOP FOR LAWNS PLUS	129081, 128974, 030019, 029802	Major	46 year old male ingested 1/3 of a bottle of herbicide. He experienced drowsiness, hypersecretions and was intubated.

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Table 3. Dicamba Incidents reported to Main IDS from 2019-July 31, 2020[xx]

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
				CRABGRASS KILLER 3			
032551 – 00032	8/27/2019	CLARKSVILLE, IN	009688-00293-008845	SPECTRACIDE WEED & GRASS KILLER 3	032201, 122809, 029802	Moderate	67 year old female used Spectracide Weed & Grass Killer 3 10 days ago. Said patient got product in both her eyes. A week later, she experienced feeling like she is "looking through liquid" and frequent headaches.
032489 – 00001*	9/4/2019	HERSHEY, PA	009688-00265-008845	SPECTRACIDE WEED & GRASS KILLER CONCENTRATE 2	122809, 029802, 032201	Death	Suicide - male ingested an entire bottle of the product.
032639 - 00012	9/4/2019	HERSHEY, PA	009688-00265-008845	SPECTRACIDE WEED & GRASS KILLER CONCENTRATE 2	029802, 032201, 122809	Moderate	60 year old male drank 1/2 bottle of product. He experienced vomiting, shortness of breath, diarrhea, confusion, auditory hallucination and delusion.
032714 - 00004	10/10/2019	PANAMA CITY, FL	009688-00265-008845	SPECTRACIDE WEED & GRASS KILLER CONCENTRATE 2	032201, 122809, 029802	Moderate	an adult male used the product which leaked on his back while spraying his yard causing irritation to his skin
032551 - 00023	8/5/2019	MANAKIN SABOT, VA	009688-00208-008845	SPECTRACIDE WEED & GRASS KILLER	122809, 032201, 029802	Moderate	a 78 year old male sprayed some Spectracide Weed & Grass Killer and he developed flu like symptoms along with a fever. He was taken to his physician and was treated with medication and felt better for about a week or so then the body aches and joint pain returned. He has preexisting heart condition and HBP. Caller states that his HBP has been much higher since exposure.
033154 - 00002	12/29/2019	LUMBERTON, NC	009688-00208-008845	UNKNOWN (SPECTRACIDE WEED & GRASS KILLER)	122809, 029802, 032201	Moderate	Consumer stated she never actually purchased the product. Consumer picked product up from the shelf, at Lowe's, and while carrying it to the counter, noticed it was leaking. By the time consumer got to the check-out counter, the product had dripped all over her clothes and was on her hand. Consumer stated, afterwards/ she went to the hospital because her hands had become irritated and red. Consumer was prescribed a prescription/ for a cream, to put on her hands and other parts of her body, where the chemical contacted.

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Table 3. Dicamba Incidents reported to Main IDS from 2019-July 31, 2020[xx]

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
032264 - 00008	5/14/2019	SYCAMORE, SC	009688-00109-008845	SPECTRACIDE WEED STOP FOR LAWNS	029802, 031520, 030019	Moderate	Caller applied to lawn in the rear and front. His daughter (5 year old) developed a rash. It started out small and now it is covering her whole body. She was taken dermatologists and pediatrician, but they were not sure what was wrong with her. She was given some medication but doesn't seem to be working. He states that it is very seldom that she plays outside, but she went out soon after he had sprayed.
032461 – 00036*	7/27/2019	SEATTLE, WA	009688-00109-008845	SPECTRACIDE WEED STOP FOR LAWNS	029802, 030019, 031520	Major	62 year old male has presented to ED and admitted with suspected organophosphate poisoning, was applying Spectracide Weed Stop for Lawns at 1 700, last known well time yesterday afternoon, ingestion vs dermal exposure, was also using 30 Seconds Outdoor cleaner. Presents with bad rash with blisters all over body with increased oral secretions, lacrimation, watery yellow diarrhea with altered mental status requiring intubation self-harm, not expected was found down by spouse later in evening
032005 - 00001	2/8/2019	VA	002217-00991-000239	WEED B GON PLUS CRABGRASS CONTROL READY-TO-USE 2	128974, 029802, 030019	Moderate	An adult male states that a few hours ago he was using this product and he thinks he may have inhaled some during use, as he now has a blister on the roof of his mouth near the back of his throat.
032486 - 00001	7/19/2019	GREENFIELD, IN	002217-00930	Q4 PLUS TURF HERBICIDE FOR GRASSY & BROADLEAF WEEDS	128974, 030019, 029802, 129081	Moderate	59 year old female was spraying product using a backpack sprayer. She said the straps got some on it when she filled it. She went in and took a shower after using it. the next morning, she woke up with hives on her arms, legs and groin. She has allergies to pollen.
032486 - 00003	7/27/2019	IL	002217-00896-000239	WEED-B-GON MAX PLUS CRABGRASS CONTROL CONCENTRATE	128974, 030019, 029802	Moderate	a senior (>64 years old) male used this product, and another yard product. The next day, he Is dizzy, has a pressure in his chest and his arms feel "tough."
032149 - 00005	3/27/2019	FORT WORTH, TX	002217-00579-072155	TRIPLE ACTION LAWN FERTILIZER PLUS WEED CONTROL	030001, 029801, 129046	Moderate	53 year old male was using these products at his home about 8 days ago and thinks he may have gotten an exposure to some of the powder when the air was blowing. He did not have long sleeves so it's possible that the product could have gotten on him. He doesn't

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Table 3. Dicamba Incidents reported to Main IDS from 2019-July 31, 2020[a]

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							remember being exposed to the product but 5 days later, he began developing a rash, itching and red skin over 50% of his body including his arms and all of his back. He has used the product in the past and he's never found himself to be allergic or sensitive to anything. The doctors aren't sure what is causing the reaction but have prescribed Kenalog Cream, Triamcinolone, Atarax and a Pyrethrin as they are also treating for a possible case of scabies.
033142 - 00001	4/8/2020	OK	000524-00617	XTENDIMAX WITH VAPORGRIP TECHNOLOGY	128931	Moderate	The warehouse manager said that Xtendimax makes his employees' noses bleed. He said he feels it is an unsafe product and he only sells it because his corporate office forces him to. He only has one experienced employee that he feels is qualified to unload Xtendimax using a special respirator.
032714 – 00013*	10/17/2019	NEW CANEY, TX	000478-00121-008845	ELIMINATOR LAWN WEED KILLER READY-TO-SPRAY	030019, 031520, 029802	Major	An adult male sent a letter to the company stating that the product caused respiratory problems and that the product was harmful, fatal to breath, and that he developed severe respiratory problems.
032543 - 00004	8/17/2019	MI	000239-02665	WEED B GON CONCENTRATE	029802, 030019, 031520	Moderate	An adult male was exposed to the product that was in the container on his back sun porch. He noticed a bad odor and experienced difficulty breathing.
032138 - 00100	4/30/2019	FL	000228-00555-000239	WEED B GON WEED KILLER FOR LAWNS READY-TO-USE2	029801, 030019, 031520	Moderate	An adult female was watching TV and there was a commercial on that said that if you have been diagnosed with cancer in relation to the weed killer to call. Caller says that she was diagnosed lung cancer 3 weeks ago. Caller says that she has been smoking for many years. Caller says that she is disabled and, in the house, alone all the time.
032490 - 00001	8/17/2019	ASTORIA, OR		ORTHO GROUND CLEAR	032202, 122809, 029801	Moderate	A duplex resident reported the use of Ortho Ground Clear (diquat, dicamba, fluazifop-p-butyl) by a neighboring owner outside her unit's open windows, resulting in lasting odors and white residue inside her home and symptoms for herself, her husband, 3-year-old son, and 5-year-old daughter. Symptoms included various skin/respiratory irritations.

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Table 4. Incident Description for Dicamba Incident Reports in CA PISP 2012-2017

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Year	Case Number (a)	Ag/Non-Ag (d)	Pesticide	Activity	Exposure Type	Application Site	Medical Description	Narrative Description
2012	350	Non-Ag	Dicamba, Mcpa, Triclopyr	Applicator	Direct Spray/Squirt	Ornamental Lawns	Some burning sensation in eyes that "felt like sand paper". Conjunctivae were minimally red. No vision changes, skin irritation, or fluorescein dye uptake. Mild hay fever was noted.	A woman prepared to apply an herbicide using a hose end sprayer, but the sprayer was not threaded to the hose correctly. When she turned on the water she was sprayed in the face and eyes.
2012	407	Non-Ag	Dicamba, Diquat, Fluazifop-P-Butyl	Applicator	Direct Spray/Squirt	Ornamental Plants (Other or Unspecified)	Initial tightness in chest and shortness of breath which prevented him from falling asleep. He has a history of asthma. A week later, he developed a fever and flu-like symptoms. His wife developed similar symptoms two days after he did.	A man used a hand pressurized sprayer to apply pesticides. The handle apparently loosened, and when he picked up the sprayer, he was shot in the face by the pressurized liquid. He sought care the next day.
2012	1118	Non-Ag	Dicamba, Mcpa, Triclopyr	Applicator	Spill/Other Direct	Ornamental Lawns	Tingling hands. A doctor noted mild redness of the hands, but also that the patient said the coloration was usual for him.	Diluted herbicide leaked onto a man's unprotected hands as he adjusted the spray tip of the wand. He completed the application in about fifteen minutes, then washed his hands. When his hands started tingling, he read the label and went for care.
2012	1134	Non-Ag	2,4-D, Dicamba, Isoxaben, Mecoprop-P	Routine Indoor	Spill/Other Direct	Not Applicable	Rash and swelling of hands in the evening after playing in the garage. Medical report describes a macular	A child may have applied an herbicide to her hands while playing in a relative's garage. Her cousin claims to have seen her put it on her fingers, and

							papular rash and lesions on fingers, with increased peeling of skin after 10 days.	she developed symptoms later that day.
2012	1240	Non-Ag	2,4-D, Dicamba, Mecopro p-P	Mechanical	Direct Spray/Squirt	Not Applicable	Red and irritated eyes. The man suggested his eyes could have been red from all the rinsing, but the herbicide is a known irritant.	A man thought the wand of his backpack sprayer wasn't working right, so he disassembled it without depressurizing the sprayer. Diluted herbicide squirted over his glasses and into his eyes. He rinsed them out and went for care.
2012	1267	Ag	Dicamba, Glyphosa te	Applicator	Drift	Agricultural & Farm Equipment (Other or Unspecified)	Dizziness, nausea, shortness of breath, vomiting, headache, abdominal cramping, and watery eyes. He continued to feel ill for several days after the exposure. Organophosphate was suspected but not identified. Cholinesterase level within normal lab range.	68-sta-12. The wind picked up as a man sprayed herbicides around irrigation valves in a dairy, which blew the product into his face. He was not trained on pesticide use, his employer said this was because he was not supposed to apply them.
2013	417	Non-Ag	2,4-D, Dicamba, Mecopro p-P, Sulfentra zone	Unknown	Direct Spray/Squirt	Unknown	Eye redness.	A man accidentally sprayed herbicide into his eyes and sought care the next day. The investigator was unable to contact the man.
2013	830	Non-Ag	Dicamba, Unknow n	Applicator	Spill/Other Direct	Surfaces (Other or Unspecified)	Redness and irritation on hands.	A man sprayed an herbicide containing dicamba and chlorophenoxy compounds around his patio and planters. He did not wear gloves, and some of the product got into his hands. He didn't wash his hands until he developed symptoms, about an hour later.

2013	1150	Non-Ag	2,4-D, Dicamba, Mecopro p-P	Routine Outdoor	Ingestion	Unknown	Vomited multiple times, fever of 38.2 c. Viral gastroenteritis was suspected.	A child's grandparent's found him with an empty bottle that had contained a small amount of herbicide. The child became ill and was taken for care. The family was unable to provide further details upon interview.
2013	1255	Non-Ag	2,4-D, Dicamba, Quinclor ac, Triclopyr	Other	Ingestion	Not Applicable	Pain with swallowing, abdominal pain, drowsiness, ataxia, nausea, sinus tachycardia with minimal st depression, hypotension (89/40), elevated serum ph, anion gap, slightly elevated liver function tests. Endoscopy showed some gastritis & esophagitis.	105-sac-14. A man ingested two herbicides in a self harm gesture. There was concern that he also ingested an anti-depressant and was undergoing alcohol withdrawal. He was hospitalized at least 4 days but lost to follow-up. No investigation was conducted.
2014	227	Ag	Adjuvant , Dicamba, Pyroxsul am	Other	Drift	Wheat	Coughing, tightness in chest, headache. Her symptoms subsided after a couple of hours of getting fresh air.	08-kin-14. A school bus carrying 16 children traveled near a field that was being treated aerially with pesticides. The bus driver & 4 children smelled a strong odor and developed symptoms, but only 3 children sought care. See also 2014-589 to 592 & 653.
2014	228	Non-Ag	2,4-D, Dicamba, Quinclor ac	Transport/S torage/Disp osal	Spill/Other Direct	Not Applicable	He reported a pesticide taste in his mouth, heart palpitations, watery eyes, runny nose, and dermal irritation.	A man purchased an herbicide. While entering his vehicle in the parking lot, a car rapidly approached and he had to sit on the pesticide to avoid being hit. The container leaked and soaked into his jeans. He showered at home about 20 minutes later.
2014	239	Non-Ag	2,4-D, Dicamba, Mecopro p-P	Other	Ingestion	Not Applicable	She was given activated charcoal, iv hydration, and iv bicarbonate. After approximately 6 hours in the ed, she had reddened, peeling skin on her face, and	A woman ingested 8-12 ounces of an herbicide in a self-harm attempt. She was taken for care. Due to the sensitive nature of this case, no investigation was conducted.

							vomited. She was hospitalized for less than one day before being transferred to psychiatric care.	
2014	383	Non-Ag	2,4-D, Dicamba, Quinclorac, Unknown	Applicator	Spill/Other Direct	Ornamental Lawns	Nausea and diarrhea. His symptoms had resolved without treatment while at the medical facility.	A teenager sprayed weeds with herbicide after mowing the lawn. Some of the chemical got onto his hands. It was windy, and he believed some may have blown onto his face as well. He did not wash his hands. A few hours later he began to feel ill.
2014	419	Non-Ag	2,4-D, Dicamba, Mecoprop-P, Quinclorac	Applicator	Direct Spray/Squirt	Ornamental Lawns	Eye irritation and redness.	A man sprayed weeds in his yard with an herbicide which was attached to a hose. When he finished, he accidentally squirted himself in the eye with the product while trying to shut off the nozzle. He thinks his finger may have been on the trigger.
2014	500	Non-Ag	2,4-D, Dicamba, Quinclorac	Other	Other	Not Applicable	Burning sensation on lip. He rinsed his mouth and was reportedly asymptomatic when he reached the emergency department.	A hardware store worker processed a customer return of an open bottle of herbicide wrapped in a plastic bag. Minutes later, a fly landed on his lip and he brushed it away with his hand, then his lip began burning and he was taken for care.
2014	589	Ag	Adjuvant, Dicamba, Pyroxsulam	Other	Drift	Wheat	Headache, burning nose and throat. His window was down. His symptoms subsided by the evening.	08-kin-14. Ref. 2014-227. The driver said the bus did not get sprayed & that she did not drive through a cloud of pesticides. She said her window was down along with other windows on the bus. No one felt any spray mist. They only smelled a strong odor.

2014	590	Ag	Adjuvant , Dicamba, Pyroxsul am	Other	Drift	Wheat	Smelled bad odor and began coughing and sneezing. Later developed a headache and felt like vomiting.	08-kin-14. Ref. 2014-227. The driver contacted the district office and was instructed to return to the school. Swab samples taken from the school bus found no detectable levels of the pesticides applied. This student sat near an open window.
2014	591	Ag	Adjuvant , Dicamba, Pyroxsul am	Other	Drift	Wheat	Headache, upset stomach.	08-kin-14. Ref. 2014-591. This student sat behind the driver. Her window was closed but the one in front of her was open. She noticed wind blowing toward them and there was a strong smell. No violations were noted during this investigation.
2015	100	Non-Ag	Dicamba, Diquat, Fluazifop -P-Butyl	Mixer/Loa der	Other	Not Applicable	Intense burning sensation in eye. He was diagnosed with conjunctivitis.	A man poured the contents of one insecticide bottle into a smaller bottle. During the process, pesticide spilled onto the container, and his hand became wet when he touched it. He washed his hands, and hours later rubbed his eye and felt discomfort.
2015	156	Non-Ag	2,4-D, Dicamba, Quinclor ac	Applicator	Direct Spray/Squirt	Household or Domestic Dwelling (Other or Unspecified)	Throat irritation, labored breathing, upper chest pain.at the ed, oxygen saturation was at 98%, and lungs were clear.	A homeowner was spraying his yard when the application valve on the bottled malfunctioned and a stream of the pesticide shot up his nose and in his eyes and mouth. He flushed eyes with water for 15 - 20 minutes. He developed symptoms 2 hours later.
2015	393	Non-Ag	Dicamba, Diquat, Fluazifop -P-Butyl	Applicator	Spill/Other Direct	Ornamental Lawns	Redness, irritation and blisters the day following application. A doctor gave a diagnosis of second and third degree burns and blisters on both hands. He had three skin graft surgeries in order to re-construct hands.	59-sd-15. A man used a measuring cup to add herbicide into a sprayer. On a 2nd addition, he used twice the rate listed on the label. While spraying, the container started to leak. He did not wear gloves. The next day, he developed symptoms and sought car

2016	117	Non-Ag	Dicamba, Diquat, Fluazifop-P-Butyl	Applicator	Unknown	Ornamental Plants (Other or Unspecified)	Stinging, red, irritated, and sore eyes. He flushed his eyes with water and sought medical care. He also sought care the next day at a different hospital because his eyes were still sore.	After applying an herbicide, a man took off his glasses, then his gloves, and washed his hands with soap and water. When he put his glasses back on, he thought some liquid may have trickled into his eyes because they began to feel irritated and sore.
2016	387	Non-Ag	Adjuvant, Aminopyralid, Chlorsulfuron, Dicamba	Applicator	Spill/Other Direct	Pastures, Rangeland, Uncultivated Non-agricultural Areas	Initial symptoms of mild, red irritation of the feet. Continual use of contaminated leather boots resulted in itchy rash, blisters, and ecchymosis. Doctor noted that it looks like contact dermatitis, also has fungal infection of toenails.	A worker applied herbicides to various locations over a 4-day period. The pesticides leaked from the spray wand onto his leather boots. He did not have the leak fixed or change out of his contaminated boots. He developed symptoms the 2nd day of spraying.
2017	258	Non-Ag	Dicamba, Diquat, Fluazifop-P-Butyl	Routine (Other or Unspecified)	Spill/Other Direct	Not Applicable	She experienced red eyes. Medical staff noted she smelled of the herbicide.	While at grandmaâ€™s house, a toddler picked up a bottle of herbicide that was accessible. As she carried the bottle, she dropped it and some of the herbicide splashed up into her eyes. Her mother immediately rinsed her eyes and took her for care.
2017	906	Non-Ag	Dicamba, Diquat, Fluazifop-P-Butyl	Other	Ingestion	Not Applicable	In the hospital, she had two bouts of vomiting and was tachycardic (heart rate 103). Laboratory results were positive for cannabinoids. She was medically cleared to psych less than 24 hours later.	A 39-year old woman ingested an herbicide and a fertilizer in a self-harm attempt. An investigation was not conducted due to the sensitive nature of the case. She showed the doctor pictures of products ingested.

2017	1109	Non-Ag	2,4-D, Dicamba, Quinclorac	Routine Indoor	Unknown	Not Applicable	He threw up on the way to the emergency room. No other symptoms were exhibited.	After use, an herbicide container was left on the washing machine. Later, a 2-year old boy climbed on the washing machine & opened the container. His father found him crying and when questioned, the boy pointed to the open herbicide container.
2017	1482	Non-Ag	Dicamba, Diquat, Fluazifop-P-Butyl	Applicator	Unknown	Surfaces (Other or Unspecified)	He experienced sneezing, body rash, red face, and difficulty speaking. In the emergency room, he felt better after he was given antihistamines and antacid with a liter of fluid.	A 44-year old man applied an herbicide to weeds emerging from the cracks and gravel in the yard. He did not feel well when he came inside the house. His wife took him to the emergency room a few hours later. His wife provided details on this incident.

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7 APPENDIX B: SUMMARY OF EPIDEMIOLOGIC STUDIES AND STUDY QUALITY ASSESSMENT

Table B-1: Summary of Epidemiologic Studies on Cancer

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results[67]	Study Quality
All Cancers							
Koutros et al. (2008)	1993-1997 (Enrollment) to 2004	AHS	Prospective Cohort n = 49,762 pesticide applicators	AHS Survey Instrument – Ever/Never DDVP Use and Cumulative Lifetime Use	Cancer registries in Iowa and North Carolina	No evidence of a positive association was reported between DDVP exposure and total cancer at all exposure tertiles with the low exposure group and the nonexposed group as the referent ($0.81 \leq RR \leq 1.01$; all 95% CIs encompassed the null value of	High

[67] For additional reported results including risk measures, number of cases/non-cases, and p-values, refer to the individual study summaries written above.

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results[67]	Study Quality
						1.0; with n = 74 – 85 cases per exposure category, all p-trends were ≥ 0.05).	
Lerro et al. (2015)	1993-1997 (Enrollment) to 2010/2011	AHS Wives of pesticide applicators	Prospective Cohort n = 30,003 wives of pesticide applicators	AHS Survey Instrument – Ever/Never DDVP Use	Cancer registries in Iowa and North Carolina	No evidence of a significant positive association was reported between DDVP exposure and total cancer risk (RR = 1.08; 95% CI: 0.86, 1.35; with n = 81 exposed cases).	Moderate
Bladder Cancer							
Koutros et al. (2016)	1993-1997 (Enrollment) to 2010/2011	AHS	Prospective Cohort n = 54,344 male pesticide applicators	AHS Survey Instrument – Ever/Never DDVP Use and Cumulative Lifetime Use	Cancer registries in Iowa and North Carolina	No evidence of a significant positive association between DDVP exposure and risk of bladder cancer (RR = 1.01; 95% CI: 0.65, 1.55) based on ever/never use. Further analyses considered intensity-weighted lifetime days of DDVP use, and when adjusting for the aforementioned factors, no evidence of a positive association between DDVP exposure and bladder cancer in either category (RR = 0.85; 95% CI: 0.47, 1.54 for the lower exposure category and RR = 0.93; 95% CI: 0.52, 1.67 for the higher exposure category, with n = 12 exposed cases in both categories and n = 253 unexposed cases) was reported, along with no evidence of increasing risk of bladder cancer with increased use of DDVP (p-trend = 0.82).	High
Breast Cancer							
Engel et al. (2005)	1993-1997 (Enrollment) to 2000	AHS	Prospective Cohort	AHS Survey Instrument – Ever/Never DDVP Use (Indirect	Cancer registries in Iowa and North Carolina,	No evidence of a significant positive association between ever use of DDVP and breast cancer incidence (RR = 1.20;	Moderate

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results[67]	Study Quality
			n = 30,145 (309 breast cancer cases)	Exposure, based on Husband Self-Report)	coded via ICD-O-2	95% CI: 0.70, 2.10 with n = 13 cases). A subset analysis conducted for wives who reported never using DDVP considered husbands' DDVP use and also observed no evidence of a significant positive association between husband's DDVP use and wife's risk of breast cancer (RR = 1.50; 95% CI: 0.90, 2.50 with 152 cases (14.0% husbands used DDVP) and 13,297 non-cases (9.2% husbands used DDVP)	
Engel et al. (2017)	1993-1997 (Enrollment) to 2010/2011	AHS Wives of pesticide applicators	Prospective Cohort n = 22,271 wives of pesticide applicators	AHS Survey Instrument – Ever/Never DDVP Use (Direct Exposure and Indirect Exposure, based on Husband Self-Report)	Cancer registries in Iowa and North Carolina	No evidence of a significant positive association between DDVP ever use and breast cancer (HR = 1.10; 95% CI: 0.70, 1.60; with n = 32 exposed cases and 712 exposed non-cases) and husband's DDVP use (wives' indirect exposure) (0.70 < HR < 1.00; all 95% CIs encompassed the null value of 1.0; with 29 exposed cases and 971 exposed non-cases).	Moderate
Lerro et al. (2015)	1993-1997 (Enrollment) to 2010/2011	AHS Wives of pesticide applicators	Prospective Cohort n = 30,003 wives of pesticide applicators	AHS Survey Instrument – Ever/Never DDVP Use	Cancer registries in Iowa and North Carolina	No evidence of a significant positive association between DDVP ever use and breast cancer (RR = 1.19; 95% CI: 0.84, 1.70).	Moderate
Childhood Cancer							
Flower et al. (2004)	1993-1997 (Enrollment)	AHS	Prospective Cohort for parents and child cases were identified retrospectively and	AHS Survey Instrument – Ever/Never DDVP Use completed by parents	Birth certificates and cancer registries in Iowa and North Carolina	No evidence of a significant positive association was observed between parental DDVP exposure and risk of childhood cancer (OR = 2.06; 95% CI: 0.86, 4.90 with n = 6 cases) based on ever/never use.	Moderate

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results[67]	Study Quality
			prospectively following parental enrollment N = 17,280 children				
Leiss and Savitz, (1995)	1976 - 1983	Denver, Colorado	Case-control study	Ever/Never DDVP Use completed through parental interview and measured via pest strip exposure	State cancer registry and through review of area hospital records	Evidence of a strong association was observed during the last 3 months of pregnancy (OR: 3.00[68]; 95% CI: 1.60, 5.70 with n = 21 cases), a positive association was observed from birth through 2 years prior to diagnosis (OR: 1.70; 95% CI: 1.20, 2.40 with n = 21 cases), and a moderately strong association was observed from 2 years prior to diagnosis through diagnosis (OR: 2.60; 95% CI: 1.70, 3.90 with n = 18 exposed cases). For brain tumors in children, evidence of a positive association was observed from the 2 years prior to diagnosis through diagnosis exposure period (OR: 1.80; 95% CI: 1.20, 2.90 with n = 9 exposed cases). No evidence of a significant positive association was observed during the other two exposure periods for brain tumors ($1.40 < OR \leq 1.50$; all CIs encompassed the null value of 1.0; with n = 10 – 13 exposed cases). Additionally, no evidence of a significant	Moderate

[68] The study reported that this odds ratio (OR = 3.00) was not adjusted, unlike the other odds ratios reported, due to missing values.

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results[67]	Study Quality
						positive association was observed for total cancers (overall) and lymphomas among children during all three of the exposure periods specified above (total cancers (overall): $1.20 < OR \leq 1.50$; all CIs encompassed the null value of 1.0; with n = 45 – 61 exposed cases, n = 26 – 47 exposed controls[69]; lymphomas: $1.10 < OR \leq 1.40$; all CIs encompassed the null value of 1.0; with n = 4 –7 exposed cases). For soft tissue sarcomas, no evidence of a positive association was observed during two exposure periods (3 months before birth, birth up to 2 years prior to diagnosis) (OR: $0.50 < OR \leq 0.60$; all CIs encompassed the null value of 1.0; with n = 2 exposed cases/category).	
Cancers of the Large Intestine							
Koutros et al. (2008)	1993-1997 (Enrollment) to 2004	AHS	Prospective Cohort n = 49,762 pesticide applicators	AHS Survey Instrument – Ever/Never DDVP Use and Cumulative Lifetime Use	Cancer registries in Iowa and North Carolina	No evidence of a significant positive association between DDVP exposure and colon cancer for any exposure category with either the non-exposed or the lowest exposed group as the referent category ($0.97 \leq RR \leq 1.53$; all 95% CIs encompassed the null value of	High

[69] For total cancers (overall), the study reported the number of exposed cases and exposed controls in the study, but *only* reported the number of exposed cases (not exposed controls) for the other cancers reported: leukemias, brain tumors, lymphomas, and soft tissue sarcomas.

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results[67]	Study Quality
						1.0; with n = 7 – 10 cases per exposure category, all p-trends were ≥ 0.05) and no evidence of a linear (monotonic) trend across categories.	
Lee et al. (2007)	1993-1997 (Enrollment) to 2002	AHS	Prospective Cohort n = 56,813 pesticide applicators	AHS Survey Instrument – Ever/Never DDVP Use	Cancer registries in Iowa and North Carolina, coded via ICD-O-2	No evidence of a significant positive association was reported between exposure to DDVP and colorectal cancer based on ever use (OR = 1.30; 95% CI: 0.80, 1.90; with n = 30 exposed cases and n = 216 unexposed cases). Similar results were observed when stratifying the analysis by colon and rectal cancer (Colon Cancer: OR = 1.50; 95% CI: 0.90, 2.40; with n = 24 exposed cases and n = 145 unexposed cases; Rectal Cancer: OR = 0.80; 95% CI: 0.40, 2.00; with n = 6 exposed cases and n = 71 unexposed cases).	High
Lung Cancer							
Bonner et al. (2017)	1993-1997 (Enrollment) to 2010 (North Carolina) & 2011 (Iowa)	AHS	Prospective Cohort n = 57,310 pesticide applicators	AHS Survey Instrument – Cumulative Lifetime DDVP Use	Cancer registries in Iowa and North Carolina	Evidence of a moderately strong association was observed for lung cancer in the lowest tertile of exposure only (HR: 2.18; 95% CI: 1.03, 4.59; with n =7 exposed cases, 423 unexposed cases), relative to the unexposed group. No evidence of a positive association was observed in the mid- and highest exposure tertile (0.63 ≤ HR ≤ 0.89; all CIs encompassed the null value of 1.0; with n = 10 - 15	Moderate

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results[67]	Study Quality
						exposed cases, p-trend = 0.855), relative to the unexposed group. For intensity-weighted lifetime days, no evidence of a significant positive association was observed in the low, mid, or highest exposure tertile (0.56 ≤ HR ≤ 1.39; all CIs encompassed the null value of 1.0; with n = 10 - 11 exposed cases, n = 423 unexposed cases, p-trend = 0.599), relative to the unexposed group, and no evidence of a statistically significant p-trend was observed	
Koutros et al. (2008)	1993-1997 (Enrollment) to 2004	AHS	Prospective Cohort n = 49,762 pesticide applicators	AHS Survey Instrument – Ever/Never DDVP Use and Cumulative Lifetime Use	Cancer registries in Iowa and North Carolina	No evidence of a significant positive association between DDVP exposure and lung cancer at any exposure tertile with the non-exposed or the lowest exposed group as the referent (0.13 ≤ RR ≤ 1.18; all 95% CIs encompassed the null value of 1.0; with n = 2 – 6 cases per exposure category, all p-trends were ≥ 0.05) and no evidence of a linear (monotonic) trend across categories.	High
Lymphohematopoietic cancers							
Koutros et al. (2008)	1993-1997 (Enrollment) to 2004	AHS	Prospective Cohort n = 49,762 pesticide applicators	AHS Survey Instrument – Ever/Never DDVP Use and Cumulative Lifetime Use	Cancer registries in Iowa and North Carolina	No evidence of a significant positive association between DDVP exposure and lymphohematopoietic cancers at any exposure level with either the non-exposed or the lowest exposed group as the referent category (0.75 ≤ RR ≤	High

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results[67]	Study Quality
						1.10; all 95% CIs encompassed the null value of 1.0; with n = 7 – 10 cases per exposure category, all p-trends were ≥ 0.05) and no evidence of a linear (monotonic) trend across categories.	
Leukemia							
Brown et al. (1990)	1980 up to 1987	Males (both farmers and nonfarmers) living in Iowa and Minnesota	Population-based case-control interview study	Self-reported DDVP use collected during in-person interviews	Tumor registry database or a special surveillance network including hospital and pathology records in Iowa and Minnesota	Evidence of a moderately strong association was reported between DDVP exposure and leukemia among farmers based on ever/never use (OR: 2.00; 95% CI: 1.20, 3.50; with n = 26 cases and n = 38 controls), with nonfarmers as the referent. Similarly, when the data was further stratified based on pesticide use at least 20 years prior to the interview,[70] evidence of a moderately strong association was reported for leukemia among farmers (OR: 2.40; 95% CI: 1.10, 5.40; with n = 12 cases and n = 15 controls).	Moderate
Non-Hodgkin's Lymphoma							
Alavanja et al. (2014)	1993-1997 (Enrollment) to 2010/2011	AHS	Prospective Cohort n = 54,306 pesticide applicators	AHS Survey Instrument – Ever/Never DDVP Use and Cumulative Lifetime Use	Cancer registries in Iowa and North Carolina	No evidence of a significant positive association any exposure category for lifetime days of exposure (0.90 ≤ RR ≤ 1.40; all 95% CIs encompassed the null value 1.0, with n = 17 – 19 cases per exposure category; p-trend = 0.78). Similarly, no evidence of a significant	High

[70] The study made no specific mention of why they chose 'at least 20 years prior to the interview', but one can interpret that the analysis that stratified the data based on pesticide handled at least 20 years ago, may have been relevant to the supplemental interview that asked farmers who reported applying pesticides, specifically, if they had applied pesticides prior to and after 1960. Perhaps, this 20-year time period was to allow for a latency period following exposure (DDVP) before the outcome (leukemia) was diagnosed.

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results[67]	Study Quality
						positive association was reported for any exposure category for intensity-weighted lifetime days of exposure and all NHL cases ($1.00 \leq RR \leq 1.40$; all 95% CIs encompassed the null value 1.0, with n = 17 – 18 cases per exposure category; p-trend = 0.83).	
Cantor et al. (1992)	1980 up to 1984	Males (both farmers and nonfarmers) living in Iowa and Minnesota	2 population-based case-control interview studies	Self-reported DDVP use collected during in-person interviews	Pathology reviews were conducted to confirm NHL and subtypes	No evidence of a significant positive association was reported between DDVP exposure and NHL among farmers based on ever/never use (OR: 1.20; 95% CI: 0.70, 2.20), relative to non-farmers	Moderate
De Roos et al. (2003)	1979 – 1983	Four Midwestern states within the United States-Iowa, Nebraska, Kansas, and Minnesota	Pooled analysis of three case-control studies N = 870 cases, 2,569 controls	Self-reported DDVP use through questionnaires administered by interviewers to study participants or proxy respondents using a series of exposure-related questions asked in various ways (e.g., directly vs. open-ended questions)	Nebraska Lymphoma Study Group and local hospitals (Nebraska); state cancer registry (Kansas & Iowa); surveillance program in hospitals and pathology laboratories (Minnesota)	No evidence of a positive association was reported between DDVP exposure and NHL for both the logistic and hierarchical regressions (OR = 0.90; 95% CI: 0.40, 2.00; OR = 0.90; 95% CI: 0.50, 1.70 with n = 16 cases)	Moderate
Leon et al. (2019)	1969, 1974, 1979, 1985, & 1989 (census data from Norwegian CNAP study) 1993 – 1997 (US AHS) through 2010 (North Carolina) & 2011 (Iowa) 2005-2007 through 2009 (French AGRICAN study)	AHS, Norwegian CNAP study, & French AGRICAN study	Prospective Cohort N = 316,270 agricultural workers included in the combined study population	Self-reported Ever/Never DDVP Use	Cancer and mortality registries and the U.S National Death Index (AHS and CNAP only) & self-report	No evidence of a significant positive association for DDVP ever exposure and overall NHL (i.e., all subtypes considered together) (OR = 1.10; 95% CI: 0.95, 1.27, with n = 523 exposed cases) in the meta-analysis.	Low

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results[67]	Study Quality
Koutros et al. (2019)	1980s (US) 1991 – 1994 (Canada)	Men in the US and Canada	Pooled analysis using four population-based case-control studies N = 1,690 cases, 5,131 controls n = 25 cases and 53 controls reported DDVP exposure	Interview-led questionnaires in-person or via the telephone or mail	Pathology reviews were conducted in each study, and NHL and subtypes were coded via ICD – O – 1 using original histology codes	No evidence of a significant positive association between DDVP and NHL, based on ever/never use (OR = 1.04; 95% CI: 0.64, 1.71; with n = 25 exposed cases and n = 53 exposed controls). Similarly, when the data was further stratified for duration of pesticide use, no evidence of a significant positive association was observed between DDVP and NHL in any tertile (< 10 years OR: 1.18; 95% CI: 0.53, 2.60 with n = 10 cases, 18 controls; ≥ 10 years OR: 0.88; 95% CI: 0.46, 1.69 with n = 14 cases, 34 controls, p-trend = 0.80), relative to the unexposed group (n = 1,496 cases, 4,131 controls). For the NHL subtypes, no evidence of a significant positive association was observed for the FL subtype (OR: 1.31; 95% CI: 0.67, 2.57 with n = 11 ever exposed cases, 457 never exposed cases) and for the 'other' subtype (OR: 1.75; 95% CI: 0.84, 3.64 with n = 9 ever exposed cases, 391 never exposed cases) For the DLBCL and SLL subtypes, odds ratios were not reported due to the number of exposed cases (n < 5 exposed cases), as indicated by the study authors.	Moderate
Waddell et al. (2001)	1981-1986 (enrollment)	National Cancer Institute -	Pooled analysis using three population-	Interview-led questionnaires in-	Pathology reviews and classification by	No evidence of a positive association was reported between DDVP exposure and	Moderate

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results[67]	Study Quality
		Kansas, Iowa, Minnesota, Nebraska;	based case-control studies	person or via the telephone or mail	Working Formula (National Cancer Institute)	NHL among a small number of cases (OR = 1.00; 95% CI 0.60, 1.70; with n = 23 exposed cases and n = 51 exposed controls), based on ever use.	
Follicular Cell Lymphoma							
Alavanja et al. (2014)	1993-1997 (Enrollment) to 2010/2011	AHS	Prospective Cohort n = 54,306 pesticide applicators	AHS Survey Instrument – Ever/Never DDVP Use and Cumulative Lifetime Use	Cancer registries in Iowa and North Carolina	No evidence of a significant positive association in any exposure category for lifetime days of exposure among a small number of cases (1.0 < RR < 1.50; all 95% CIs encompassed the null value 1.0, with n = 3 - 5 cases per exposure category; p-trend = 0.90).	High
Leon et al. (2019)	1969, 1974, 1979, 1985, & 1989 (census data from Norwegian CNAP study) 1993 – 1997 (US AHS) through 2010 (North Carolina) & 2011 (Iowa) 2005-2007 through 2009 (French AGRICAN study)	AHS, Norwegian CNAP study, & French AGRICAN study	Prospective Cohort N = 316,270 agricultural workers included in the combined study population	Self-reported Ever/Never DDVP Use	Cancer and mortality registries and the U.S National Death Index (AHS and CNAP only) & self-report	No evidence of a significant positive association was reported for DDVP exposure and follicular cell lymphoma (HR = 1.10, 95% CI: 0.69, 1.76)	Low
Other Non-Hodgkin Lymphoid Malignancies							
Alavanja et al. (2014)	1993-1997 (Enrollment) to 2010/2011	AHS	Prospective Cohort n = 54,306 pesticide applicators	AHS Survey Instrument – Ever/Never DDVP Use and Cumulative Lifetime Use	Cancer registries in Iowa and North Carolina	Evidence of a moderately strong positive association was reported between lifetime-days of DDVP use and multiple myeloma NHL subtype in the low exposure category but not in the high exposure category (Low - RR = 2.70; 95% CI:	High

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results[67]	Study Quality
						1.20, 5.80; with n = 7 exposed cases; High - RR = 1.00; 95% CI: 0.30, 2.70; with n = 4 exposed cases; p-trend 0.81), and no evidence of an exposure-response trend was reported. No evidence of a significant positive association was reported for lifetime-days of DDVP exposure and the other NHL-subtypes for both the low and high exposure categories (0.70 < RR < 1.5; all 95% CIs encompassed the null value of 1.00; with 3 – 6 exposed cases per exposure category, all p-trends > 0.05) and no NHL subtype showed evidence of an exposure-response trend.	
Leon et al. (2019)	1969, 1974, 1979, 1985, & 1989 (census data from Norwegian CNAP study) 1993 – 1997 (US AHS) through 2010 (North Carolina) & 2011 (Iowa) 2005-2007 through 2009 (French AGRICAN study)	AHS, Norwegian CNAP study, & French AGRICAN study	Prospective Cohort N = 316,270 agricultural workers included in the combined study population	Self-reported Ever/Never DDVP Use	Cancer and mortality registries and the U.S National Death Index (AHS and CNAP only) & self-report	No evidence of a significant positive association was reported for the association between DDVP ever-exposure and any NHL subtype (0.94 < HR < 1.07; all CIs encompassed the null value of 1.0, with 81 – 116 cancer cases per type of cancer).	Low
Prostate Cancer							
Barry et al. (2011), Barry et al. (2012)	1993-1997 (Enrollment) to 2004	AHS	Nested case-control n = 776 cases, n = 1,444 controls	AHS Survey Instrument – Ever/Never DDVP Use and Cumulative Lifetime Use	Cancer registries in Iowa and North Carolina	No evidence of a positive association between DDVP exposure and prostate cancer in either the low or high exposure categories, with the non-exposed group as the referent (Low – OR = 0.90; 95% CI: 0.62, 1.32, with 44 cases and	High

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results[67]	Study Quality
						91 controls; High – OR = 0.82; 95% CI: 0.56, 1.21, with 40 cases and 91 controls; p-trend = 0.32).	
Christensen et al. (2016)	Enrollment (1993 – 1997) and 2004	AHS	Nested case-control n = 776 cases, n = 1,444 controls	AHS Survey Instrument – Ever/Never DDVP Use and Cumulative Lifetime Use	Cancer registries in Iowa and North Carolina	No evidence of a positive association was reported between DDVP exposure and prostate cancer among white male pesticide applicators in either the low or high exposure categories, with the non-exposed group as the referent (Low – OR = 0.81; 95% CI: 0.55, 1.20, with n = 42 exposed cases; High – OR = 0.85; 95% CI: 0.58, 1.24, with n = 44 exposed cases; p-trend = 0.428).	High
Koutros et al. (2008)	1993-1997 (Enrollment) to 2004	AHS	Prospective Cohort n = 49,762 pesticide applicators	AHS Survey Instrument – Ever/Never DDVP Use and Cumulative Lifetime Use	Cancer registries in Iowa and North Carolina	No evidence of a positive association was reported for DDVP exposure and prostate cancer for any other exposure tertile with either the non-exposed or the lowest exposed group as the referent category ($0.75 \leq RR \leq 0.99$; all 95% CIs encompassed the null value of 1.0; with n = 37 – 38 cases per exposure category, all p-trends were ≥ 0.05).	High
Koutros et al. (2011)	1993-1997 (Enrollment) to 2004	AHS	Nested case-control, n = 776 cases, n = 1,444 controls	AHS Survey Instrument – Ever/Never DDVP Use and Cumulative Lifetime Use	Cancer registries in Iowa and North Carolina	No evidence of a positive association was reported between DDVP exposure and prostate cancer in either the low or high exposure categories (Low - OR = 0.81; 95% CI: 0.55, 1.20 with 42 exposed cases and 90 exposed controls; High ¬ OR = 0.85; 95% CI: 0.58, 1.24 with 44 exposed	High

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results[67]	Study Quality
						cases and 93 exposed controls), with p-trend = 0.428.	
Koutros et al. (2013)	1993-1997 (Enrollment) to 2007	AHS	Prospective Cohort n = 54,412 pesticide applicators	AHS Survey Instrument – Cumulative DDVP Use	Cancer registries in Iowa and North Carolina	No evidence of a significant positive association was observed for prostate cancer and for aggressive prostate cancer relative to DDVP exposure for any of the stratified exposure categories ($0.85 \leq RRs \leq 1.15$; all CIs encompassed the null value of 1.00) and there was no evidence of a linear (monotonic) trend across categories for total prostate cancer and aggressive prostate cancer (p-trends = 0.50, 0.80).	Moderate
Mills and Yang, (2003)	1987 – 1999	United Farm Workers of America (UFW)	Nested case-control study N = 222 prostate cancer cases	Records to verify occupational history, grower's contracts to establish the crop/commodity the member was exposed to, and the pesticide use records (PUR) from the California Department of Pesticide Regulation	State cancer registry files	No evidence of a significant positive association was reported for DDVP at the high exposure level, relative to the low exposure group as the referent among farmers (OR high: 1.35; 95% CI: 0.93, 1.96, and when exposure was further stratified by quartile of DDVP use, with the low exposure group as the referent ($1.15 \leq OR \leq 1.64$; CIs encompassed	Moderate

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results[67]	Study Quality
				to determine DDVP cumulative use		the null value of 1.00 for all exposure categories; p-trend = 0.21)	

Table B-2: Summary of Epidemiologic Studies on Other Health Outcomes

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results	Study Quality
Autoimmune Disease							
Parks et al. (2019)	1993-1997 (enrollment) 1999 – 2003 2005–2010 (5-Year and 10-Year Follow-Up)	Biomarkers of Exposure and Effect in Agriculture (BEEA) study within the AHS	Prospective Cohort N = 699 male private pesticide applicators	Self-reported cumulative use of DDVP	Blood samples collected and measured for antibodies via laboratory testing Presence of the following antibodies in blood serum: Anti-nuclear antibodies (ANA), extractable nuclear antibodies (ENA) and anti-dsDNA antibodies	No evidence of a significant positive association was reported for lifetime use of DDVP and Higher ANA with the no detectable ANA group as the referent (OR = 1.02; 95% CI: 0.50, 2.11; with n = 10 exposed out of 60 cases of Higher ANA). And, no evidence of a positive association was reported for either Any ANA or Moderate-higher ANA with the no detectable ANA group as the referent ($0.80 \leq OR \leq 0.85$; all 95% CIs encompassed the null value of 1.0; with n = 23 – 66 exposed cases of ANA among 79 - 140 unexposed cases of ANA at each positivity level)	Moderate
Birthweight							

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results	Study Quality
Sathyanarayana et al. (2010)	1993-1997 (enrollment)	AHS	Cross-Sectional n = 2,246 female spouses who had a singleton birth within 5 years of AHS enrollment	AHS Survey Instrument – Ever/Never DDVP Use	Study subjects reported the weight in pounds and ounces for each most recent birth	No evidence of a significant reduction was reported between mother's ever use of DDVP and a change in offspring's birth weight (regression estimate coefficient = -50 grams; 95% CI: -203, 104 grams)	Low
Depression							
Beard et al. (2013)	1993-1997 (enrollment) to 2005-2010 (follow-up)	AHS	Prospective Cohort N = 16,893 female spouses	AHS Survey Instrument – Ever/Never DDVP Use Self-reported	Self-reported incident depression between the time of study enrollment (1993-1997) to study follow-up (2005-2010)	No evidence of a significant positive association was reported for wives' DDVP ever use and self-reported incident depression (RR = 1.05; 95% CI: 0.71, 1.56; with n = 27 exposed cases,) and no evidence of a positive association was reported for husband's ever use of DDVP and self-reported incident depression among wives' who never used DDVP (RR = 0.97; 95% CI: 0.69, 1.38; with 39 cases with indirect exposure)	Moderate

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results	Study Quality
Beard et al. (2014)	1993-1997 (enrollment) to 2005-2010 (follow-up)	AHS	Prospective Cohort N = 21,208 male applicators	AHS Survey Instrument – Ever/Never DDVP Use Self-reported	Self-reported incident depression between the time of study enrollment (1993-1997) to study follow-up (2005-2010)	No evidence of a significant positive association was reported between DDVP exposure and risk of depression for those who reported depression at enrollment only (OR = 1.10; 95% CI: 0.80, 1.50) or for those who reported depression at follow-up only (OR = 1.30; 95% CI: 1.00, 1.60). Evidence of a statistically significant positive association between DDVP exposure and risk of depression was reported for those reporting depression at both enrollment and follow-up (OR = 1.60; 95% CI: 1.30, 2.10); however, Wald chi-square tests found no significant difference in the ORs between these time of diagnosis groups (p = 0.11)	Moderate
Diabetes							
Juntarawijit and Juntarawijit, (2018)	February – May 2016	Bangkok, Thailand 7 of 21 area hospitals participated	Population-based case-control study N = 1,887 male pesticide applicators	Self-reported questionnaire orginating from the Agricultural Health Study[71], and led by a group of trained interviewers (~50 interviewers/village, 5 – 10/village)	Cases were medically diagnosed from area hospitals that were randomly selected to be part of the study	No evidence of a significant positive association was reported for diabetes based on ever/never DDVP exposure (adjusted OR: 1.03; 95% CI: 0.41, 2.62 n = 10 cases, 12 controls)	Moderate

[71] https://aghealth.nih.gov/collaboration/questionnaires.html

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results	Study Quality
Montgomery et al. (2008)	1993-1997 (enrollment) to 1999-2003 (follow-up)	AHS	Prospective Cohort n = 33,457 (1,176 Diabetes Cases)	AHS Survey Instrument – Ever/Never DDVP Use Self-reported	Self-reported diabetes between the time of study enrollment (1993-1997) to study follow-up (1999-2003)	No evidence of a positive association was reported between DDVP and diabetes (OR = 0.92; 95% CI: 0.75, 1.13; with n = 110 exposed cases and n = 3,105 exposed non-cases) based on ever use when adjusted for age only. Similarly, further adjusting the model for state of residence and BMI in addition to age, no evidence of a positive association was reported (OR = 1.21; 95% CI: 0.98, 1.49; with n = 110 exposed cases and n = 3,105 exposed non-cases) and for the dose-response relationship between lifetime cumulative days of DDVP use and risk of diabetes (1.15 ≤ OR ≤ 1.26; all 95% CIs encompassed the null value of 1; with n = 30 - 44 cases per exposure category; all p-values ≥ 0.05) with the no exposure group as the referent and no evidence of an increasing exposure-response trend was reported (Wald's chi square p-trend = 0.15).	Moderate
Starling et al. (2014)	1993-1997 (enrollment) and at least one of the two follow-up interviews at 5-years or 10-years after enrollment	AHS	Prospective Cohort female spouses (n = 13,637) of farmers	AHS Survey Instrument Ever/Never DDVP Use	Self-reported a physician-diagnosis of diabetes after enrollment, and who had complete information on BMI	No evidence of a positive association was reported between DDVP ever use and incident diabetes in women (HR = 0.96; 95% CI: 0.70, 1.33)	Moderate
Dream Enacting Behavior							

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results	Study Quality
Shrestha et al. (2018a)	1993-1997 (Enrollment) to 2013-2015 (Phase 5 Follow-up)	AHS	Prospective Cohort n = 23,478 subjects completing Phase 5 Questionnaire	AHS Survey Instrument – Ever/Never DDVP Use	AHS Survey Instrument – , "Have you ever been told, or suspected yourself, that you seem to 'act out dreams' while sleeping?" If they answered yes, they were prompted to answer additional questions on the frequency of symptoms.	Evidence of a positive association between ever/never use of DDVP and dream enacting behavior (DEB) (OR: 1.40, 95% CI: 1.20, 1.60, n = 223 exposed cases)	Moderate
End State Renal Disease							
Lebov et al. (2015)	1993-2011 (Enrollment) to 2011	AHS	Prospective Cohort n = 31,142 wives of licensed applicators	Husband's Responses to AHS Survey Instrument Ever/Never DDVP Use and Cumulative Lifetime Use	Linkage with the United States Renal Data System and the National Death Index	No evidence of a significant positive association between indirect DDVP exposure and ESRD was reported (HR = 2.03; 95% CI: 0.99, 4.15 with n = 9 cases) based on ever use. Further analyses considered husbands' cumulative lifetime use of DDVP and ESRD among wives who reported no (personal direct) pesticide use and found no evidence of an exposure-response trend(p-trend = 0.13)	Moderate

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results	Study Quality
Lebov et al. (2016)	1993-1997 (Enrollment) to 2011	AHS	Prospective Cohort n = 55,580 Licensed male applicators	AHS Survey Instrument Ever/Never DDVP Use and Cumulative Lifetime Use	Linkage with the United States Renal Data System and the National Death Index	No evidence of a positive association using the non-exposed as the referent category: Low Exposure Category (< 3136 days: HR = 0.78; 95% CI: 0.41, 1.47; with n = 10 exposed cases and n = 2,987 exposed non-cases) High Exposure Category (≥ 3136 days: HR = 1.41; 95% CI: 0.74, 2.6; with n = 10 exposed cases and n = 1,682 exposed non-cases), with p-trend = 0.286.	High
Eye disorders							
Kirrane et al. (2005)	1993-1997	AHS	Cross-sectional n = 31,173 wives of pesticide applicators	AHS Survey Instrument – Ever/Never DDVP Use	AHS Survey Instrument – Self-reported retinal or macular degeneration	No evidence of a significant positive association between DDVP exposure and eye disorders (OR = 1.10; 95% CI: 0.50, 2.20).	Low

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results	Study Quality
Montgomery et al. (2017)	1993-1997	AHS	Nested Case-Control n = 161 cases, 39,108 controls	AHS Survey Instrument – Ever/Never DDVP Use	Cases were ascertained by physicians with supporting pathology or retinal photographs	Evidence of a positive association was reported between DDVP and AMD based on ever/never exposure (OR: 1.80; 95% CI: 1.10, 3.00; with n = 18 cases and n = 3,121 controls). The analysis of cumulative days of use of DDVP and AMD, indicated no evidence of a significant positive association for either exposure category (> 0 - 10 days, > 10 days exposure) (1.10 ≤ OR ≤ 1.90; all CIs encompassed the null value of 1; with n = 5 - 6 exposed cases per category; p-trend = 0.558) and no evidence of an exposure-response trend.	High
Fatal Injury							
Waggoner et al. (2013)	1993-1997 (Enrollment) to 2008	AHS	Prospective Cohort n = 51,035 licensed male applicators	AHS Survey Instrument – Ever/Never DDVP Use	Annual linkage with death registries in NC and IA and the National Death Index. Injury deaths defined by ICD codes indicating a fatal injury.	No evidence of a significant positive association between risk of fatal injury and DDVP exposure among male farmers in the AHS, based on ever/never use (HR: 1.02; 95% CI: 0.69; 1.50; with n = 29 exposed cases).	Low
Hearing Loss							

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results	Study Quality
Crawford et al. (2008)	1993-1997 (Enrollment) to Five-Year Follow-Up	AHS	Prospective Cohort n = 14,229 licensed male applicators	AHS Survey Instrument – Ever/Never DDVP Use as well as frequency and duration of use	Self-reported hearing loss	No evidence of a significant positive association between hearing loss and cumulative lifetime days of DDVP exposure was reported (OR = 1.08; 95% CI: 0.91, 1.25 for the low exposure group; OR = 1.16; 95% CI: 1.00, 1.36 for the high exposure group, p-trend = 0.06)	Moderate
Myocardial Infarction							
Mills et al. (2009)	1993-1997 (enrollment) to 1999-2005	AHS	Prospective Cohort n = 54,609 non-fatal MI group, 32,024 non-fatal MI group after 5-year follow-up period	AHS Survey Instrument – Ever/Never DDVP Use	Fatal MI ascertained using state and national death databases Non-fatal MI ascertained AHS Survey Instrument	No evidence of a significant positive association was reported for either fatal or non-fatal MI and DDVP exposure based on ever/never use (HR= 1.10; 95% CI: 0.78, 1.54; HR= 1.02; 95% CI: 0.79, 1.32)	Moderate
Nervous System Function							
Starks et al. (2012a)	1993-1997 (Enrollment) 2007 (Phase II, 10-year Follow-Up)	AHS	Prospective Cohort n = 1,807 licensed male applicators (eligible), 701 (participated)	AHS Survey Instrument – Ever/Never DDVP Use; lifetime days of use	Neurobehavioral function was determined through nine tests to assess central nervous system (CNS) function, along with a questionnaire	No evidence of a statistically significant association was reported for DDVP exposure and any neurobehavioral tests for DDVP ever use and for log transformed cumulative lifetime days of use ($-0.63 \leq$ all $\beta \leq 1.53$, all $p \geq 0.05$ for the associated model of DDVP regression coefficients)	Low

Starks et al. (2012b)	1993-1997 (Enrollment) Two 5-year follow-up telephone interviews (Phase 2 & 3)	AHS	Prospective Cohort n = 678 licensed male applicators	AHS Survey Instrument – Ever/Never DDVP Use; lifetime days of use was the sum of days of use calculated for each interview period	Neurological testing along with a questionnaire; the peripheral nervous system (PNS) function tests included a neurological physical exam, electrophysiological tests, and quantitative functional tests	Evidence of a moderately strong positive associations between DDVP and tandem gait and toe proprioception abnormalities and evidence of a significant positive association between DDVP and toe vibration for ever use was reported. Results from the dose-response model indicated evidence of strong association between log-transformed lifetime days of use of DDVP and toe proprioception for the low exposure group and a moderately strong association between log-transformed lifetime days of use of DDVP and tandem gait for the low and high exposure groups, with the no exposure group as the referent. A significant monotonic exposure-response trend was also reported for tandem gait, toe proprioception, and toe vibration . No evidence of a significant positive association or trend was reported for any of the other neurological physical examination tests of ankle reflex, postural tremor, and Romberg for ever use and from the log-transformed lifetime days of use of DDVP. For the analysis of DDVP exposure and the electrophysiological tests, evidence of a significant association was reported for ever use of DDVP and distal motor latency; no evidence of a significant association was reported for distal motor latency for lifetime days of	Low

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results	Study Quality
						use nor for any of the other three electrophysiological tests including distal motor amplitude, nerve conduction velocity, short F-wave latency and either ever use or lifetime days of use of DDVP. For the analysis of DDVP exposure and the quantitative functional PNS tests, no evidence of a significant association was reported for ever use of DDVP and for log-transformed lifetime days of DDVP and sway speed with eyes opened and closed, hand strength and vibrotactile threshold.	
Parkinson's Disease							
Kamel et al. (2007)	1993-1997 (Enrollment) 1999-2003 (Phase 2 Follow-up)	AHS	Cohort Cross-sectional n = 84,738 enrolled, 57,251 Phase 2 Follow-up	AHS Survey Instrument – Ever/Never DDVP Use	AHS Survey Instrument At enrollment and follow-up, "Has a doctor ever told you that you had been diagnosed with Parkinson's disease?"	No evidence of a positive association between DDVP exposure and prevalent and incident Parkinson's disease was observed based on ever/never use (OR = 0.80; 95% CI: 0.40, 1.90 for prevalent PD; OR = 0.70; 95% CI: 0.30, 1.40 for incident PD)	Moderate
Rheumatoid Arthritis							

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results	Study Quality
De Roos et al. (2005)	1993 – 1997 (Enrollment) 1999 – 2003 (5-Year Follow-Up)	AHS	Nested case-control study N = 135 female cases	AHS Survey Instrument – Ever/Never DDVP Use	Self-reported physician-diagnosed Rheumatoid arthritis Physician confirmed	No evidence of a significant positive association was reported between DDVP exposure and RA in female spouses (OR = 1.40; 95% CI: 0.50, 3.90; with n = 5 exposed cases and n = 19 exposed controls)	Low
Meyer et al. (2017)	1993 – 1997 (Enrollment) 1999 – 2003, 2005 – 2010, and/or 2013 – 2015 (Follow-Up)	AHS	Prospective cohort n = 26,134 male AHS study participants	AHS Survey Instrument – Ever/Never and cumulative DDVP use	Self-reported or physician diagnosed rheumatoid arthritis	No evidence of a significant positive association was reported between DDVP exposure and incident RA cases among male pesticide applicators (OR = 1.40; 95% CI: 0.91, 2.14). For intensity-weighted lifetime days of use, no evidence of a significant positive association was observed at any exposure tertile ($1.14 \leq OR \leq 1.76$; all 95% CIs encompassed the null value of 1; with n = 7 – 9 exposed cases/tertile; p-trend = 0.11).	Moderate
Parks et al. (2016)	1993 – 1997 (Enrollment) 1999 – 2003 2005–2010 (Phases 2&3; 5-Year and 10-Year Follow-Up)	AHS	Nested case-control study N = 24,293 female cases	AHS Survey Instrument – Ever/Never DDVP Use	Self-reported physician-diagnosed Rheumatoid arthritis Physician confirmed	No evidence of a significant positive association between DDVP exposure and all (incident and prevalent) RA cases (OR = 1.10; 95% CI: 0.56, 2.40 for total RA with n = 8 cases)	Moderate
Respiratory Effects							
Asthma							

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results	Study Quality
Henneberger et al. (2014)	1993-1997 (Enrollment)	AHS	Cross-Sectional n = 926 commercial and private applicators	AHS Survey Instrument – Ever/Never DDVP Use	AHS Survey Instrument: Self-report of a doctor's diagnosis of asthma	No evidence of a positive association was reported between exacerbated asthma and current DDVP exposure among applicators (OR = 0.80; 95% CI: 0.30, 2.60).	Low
Hoppin et al. (2008)	1993-1997 (Enrollment)	AHS	Cross-Sectional n = 25,814 farm women	AHS Survey Instrument – Ever/Never DDVP Use	AHS Survey Instrument: Self-report of a doctor's diagnosis of asthma after age 19 years and atopic status based on a self-reported history of doctor-diagnosed eczema or hay fever.	No evidence of a significant positive association for DDVP exposure for either atopic (OR = 1.35; 95% CI: 0.69, 2.66; with n = 9 exposed atopic cases) or non-atopic asthma atopic (OR = 1.25; 95% CI: 0.73, 2.11; with n = 15 exposed non-atopic cases), based on ever/never use.	Low
Hoppin et al. (2009)	1993-1997 (Enrollment) and through second mailed questionnaire	AHS	Cross-Sectional n = 19,704 male applicators	AHS Survey Instrument – Ever/Never DDVP Use	AHS Survey Instrument: Self-report of a doctor's diagnosis of asthma	No evidence of a significant positive association between ever use of DDVP and allergic asthma or non-allergic asthma, respectively (OR = 1.47; 95% CI: 0.90, 2.39 for allergic asthma and OR = 1.05; 95% CI: 0.74, 1.49 for non-allergic asthma)	Low
Chronic Bronchitis							

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results	Study Quality
Hoppin et al. (2007)	1993-1997 (Enrollment)	AHS	Cross-sectional n = 20,908 male applicators	AHS Survey Instrument – Ever/Never DDVP Use	AHS Survey Instrument: "Has a DOCTOR ever told you that you had (been diagnosed with) chronic bronchitis? If yes, how old were you when a doctor first told you? < 20, 20–39, 40–59, 60+)"	Evidence of a positive association between DDVP exposure and chronic bronchitis among male pesticide applicators (OR = 1.36; 95% CI: 1.06, 1.73; with n = ~85 – 86 exposed cases and n = ~ 2,227 – 2,228 exposed non-cases). When adjusted for correlated pesticides, no evidence of a significant positive association between DDVP exposure and chronic bronchitis among pesticide applicators (OR = 1.15; 95% CI: 0.87, 1.51).	Low

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results	Study Quality
Rinsky et al. (2019)	1993 – 1997 (Enrollment) 1999 – 2003 (Follow-Up Interview) 2005 – 2010	AHS	Prospective cohort n = 22,491 male AHS study participants	AHS Survey Instrument – Ever/Never DDVP Use	Follow-up interview, farmers were asked, "Have you ever been diagnosed with chronic bronchitis, emphysema, and COPD" in three separate questions	Evidence positive association was reported for DDVP ever use and chronic bronchitis symptoms alone (OR = 1.39; 95% CI: 1.16, 1.66, with 144 exposed cases). No evidence of a significant positive association was reported for DDVP ever exposure and COPD with chronic bronchitis and no evidence of a positive association was reported for COPD diagnosis alone (*COPD with chronic bronchitis* – OR = 1.26; 95% CI: 0.88, 1.81, with 34 exposed cases; *COPD diagnosis alone* – OR = 0.97; 95% CI: 0.79, 1.20, with 86 exposed cases) For lifetime days of use, lifetime days of DDVP use were divided into the following categories: 0 days, 1-50 days, and 50.75 – 8,350 lifetime days of use. Evidence of a positive association was reported for the highest exposure category (50.75 – 8,350 lifetime days of use)of the COPD-related outcome of chronic bronchitis symptoms only (OR = 1.35; 95% CI: 1.05, 1.73, with 80 exposed cases and 811 unexposed cases)	Low

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results	Study Quality
Valcin et al. (2007)	1993 – 1997 (Enrollment)	AHS	Prospective cohort n = 21,541 female AHS study participants	AHS Survey Instrument – Cumulative DDVP Use	Self-reported doctor diagnosis from answering the following question, "Have you ever been diagnosed with chronic bronchitis, emphysema, and COPD"	Evidence of a statistically significant positive association between DDVP and chronic bronchitis using a logistic regression model was reported (OR = 1.83; 95% CI: 1.20, 2.80 when adjusted for age and state, with n = 23 cases).	Low
Rhinitis							
Slager et al. (2010)	1993-1997	AHS	Cross-Sectional n = 21,958 private applicators	AHS Survey Instrument – Ever/Never DDVP Use	AHS Survey Instrument: Current rhinitis, self-report	Evidence of a statistically significant positive association between current DDVP use and rhinitis (OR = 1.15; 95% CI: 1.03, 1.28) based on ever/never use.	Low
Wheeze							
Hoppin et al. (2002)	1994-1997 (Enrollment)	AHS	Cross-sectional n = 20,468	AHS Survey Instrument Ever/Never DDVP Use	AHS Survey Instrument: Wheeze in past 12 months, self-report	No evidence of a significant positive association between DDVP exposure and the wheeze among pesticide applicators (OR = 1.14; 95% CI: 0.90, 1.44) based on ever use in the past year. Further, the authors reported no evidence of a linear (monotonic) trend across categories based on five ordinal categories of exposure (p-trend = 0.30).	Low

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results	Study Quality
Hoppin et al. (2006a)	1993-1997 (Enrollment)	AHS	Cross-sectional n = 20,175 (17,920 farmers and 2,255 commercial applicators)	AHS Survey Instrument – Ever/Never DDVP Use	AHS Survey Instrument: "How many episodes of wheezing or whistling in your chest have you had in the past 12 months?"	No evidence of a significant positive association was observed for wheeze among farmers (OR = 1.13; 95% CI: 0.88, 1.46 with n ~ 537 – 538 cases). Evidence of a moderately association was observed among commercial applicators (OR = 2.48; 95% CI: 1.08, 5.66 with n ~ 22 – 23 cases).	Low
Hoppin et al. (2006b)	1993-1997 (Enrollment)	AHS	Cross-sectional n = 2,255 commercial applicators from Iowa	AHS Survey Instrument – Ever/Never DDVP Use	AHS Survey Instrument: Wheeze in past 12 months, self-report	Evidence of a moderately strong association between current DDVP use and wheeze for commercial applicators based on ever/never use[72] (OR = 2.48; 95% CI: 1.08, 5.66 with n = 9 cases).	Low
Stroke							
Rinsky et al. (2013)	1993-1997 (Enrollment) Follow-up through 2008	AHS	Prospective cohort n = 51,603 AHS study participants	AHS Survey Instrument – Ever/Never DDVP Use	Vital status was ascertained at follow-up using death records	No evidence of a significant positive association between DDVP exposure and the risk of stroke mortality based on ever/never use (HR = 1.11; 95% CI: 0.70, 1.74)	Moderate
Suicide							
Beard et al. (2011)	1993-1997 (Enrollment) Follow-up through May 2009	AHS	Prospective cohort n = 81,998 AHS study participants	AHS Survey Instrument – Ever/Never DDVP Use	Vital status was ascertained using death records	No evidence of a significant positive association was reported between DDVP exposure and suicide (HR = 1.05; 95% CI: 0.51, 2.18 with n = 8 cases) based on ever/never use	Moderate

[72] The study reported that frequency of use data for DDVP was limited and as a result, dose-response data was not provided for this pesticide.

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results	Study Quality
Thyroid Disease							
Goldner et al. (2010)	1993-1997 (Enrollment)	AHS	Cross-sectional n = 16,529	AHS Survey Instrument – Ever/Never DDVP Use	AHS Survey Instrument: Self-reported history of physician diagnosed thyroid disease (hyperthyroid, hypothyroid, other)	No evidence of a positive association between DDVP exposure and hyperthyroid disease (OR = 0.62; 95% CI: 0.27, 1.4; with n = 6 exposed cases). Similarly, no evidence of a positive between DDVP exposure and hypothyroid disease or other thyroid disease (Hypothyroid disease- OR = 0.60; 95% CI: 0.37, 0.97; with n = 18 exposed cases; Other thyroid disease (OR = 0.73; 95% CI: 0.40, 1.3; with n = 11 exposed cases).	Low
Goldner et al. (2013)	1993 – 1997 (Enrollment) 1999 – 2003 (Follow-Up Phase II) 2005 – 2010 (Follow-Up Phase III)	AHS	Prospective cohort n = 22,246 male AHS study participants	AHS Survey Instrument – Ever/Never DDVP Use	Self-reported diagnosis of thyroid disease between time of study enrollment (1993-1997) to study follow-up (1999-2003, 2005 – 2010)	No evidence of a significant positive association was reported between exposure to DDVP and hypothyroid disease, based on ever/never use (OR = 1.26; 95% CI: 0.97, 1.64; with n = 69 exposed cases and n = 2,414 exposed non-cases)	Moderate
Shrestha et al. (2018b)	1993 – 1997 (Enrollment) 1999 – 2003 (Follow-Up Phase II) 2005 – 2010 (Follow-Up Phase III) 2013 – 2016	AHS	Prospective cohort n = 24,092 female AHS spouses	AHS Survey Instrument – Ever/Never DDVP Use	Self-reported diagnosis of thyroid disease using medical records for validation between time of study enrollment (1993-1997) to study follow-up (1999-	No evidence of a positive association was reported for DDVP exposure among female spouses of applicators for hyperthyroid disease based on ever use (HR Hyperthyroid: 0.77; 95% CI: 0.42, 1.41 with n = 11 exposed cases, 491 unexposed cases),	Moderate

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results	Study Quality
	(Follow-Up Phase IV)				2003, 2005 – 2010, 2013 - 2016)	and in an additional analysis that only included thyroid cases as defined by receipt of treatment in AHS spouses, reported no evidence of a positive association between DDVP exposure and hyperthyroid disease (HR: 0.92; 95% CI: 0.49, 1.72 with n = 10 exposed cases, 376 unexposed cases) No evidence of a positive association was reported for DDVP exposure and hypothyroid disease among female spouses of applicators (HR Hypothyroid: 0.83; 95% CI: 0.61, 1.14 with n = 41 exposed cases, 1,505 unexposed cases), and in an additional analysis that only included thyroid cases as defined by receipt of treatment in AHS spouses (HR: 0.88; 95% CI: 0.64, 1.21 with n = 40 exposed cases, 1,345 unexposed cases).	
Shrestha et al. (2018c)	1993 – 1997 (Enrollment) 1999 – 2003 (Follow-Up Phase II) 2005 – 2010 (Follow-Up Phase III)	AHS	Prospective cohort n = 34,879 male AHS study participants	AHS Survey Instrument – Ever/Never DDVP Use	Self-reported diagnosis of thyroid disease using medical records or questionnaire data for validation between time of study enrollment	Evidence of a positive association was reported between DDVP exposure and hypothyroid disease among private applicators (HR Hypothyroid: 1.42; 95% CI: 1.17, 1.72, p-value < 0.01) based on ever/never use and	Moderate

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary DDVP Results	Study Quality
	2013 – 2016 (Follow-Up Phase IV)				(1993-1997) to study follow-up (1999-2003, 2005 – 2010, 2013 - 2016)	for intensity-weighted lifetime days of use in the low and mid tertiles (*>0 - ≤ 539 days* - HR: 1.47; 95% CI: 1.08, 2.00; with n = 45, p-value = 0.01); *>539 days - ≤3,915 days* - HR: 1.60; 95% CI: 1.19, 2.15 n = 49, p-value = 0.00); no evidence of a significant positive association was reported in the highest exposure category (*> 3,915 days* - HR: 1.25; 95% CI: 0.89, 1.75 n = 36, p-value = 0.20), and no evidence of a significant p-trend (p-trend = 0.20)	
Shrestha et al. (2019)	1993 – 1997 (Enrollment) 1999 – 2003 (Follow-Up Phase II) 2005 – 2010 (Follow-Up Phase III) 2013 – 2016 (Follow-Up Phase IV)	AHS	Prospective cohort n = 35,150 male AHS study participants	AHS Survey Instrument – Ever/Never DDVP Use	Self-reported diagnosis of thyroid disease using medical records or questionnaire data for validation between time of study enrollment (1993-1997) to study follow-up (1999-2003, 2005 – 2010, 2013 - 2016)	No evidence of a positive association between DDVP and hyperthyroidism among private applicators was reported in both the overall analysis (n = 35,150) and stricter case analysis (n = 34,463) (*overall* – HR: 0.96; 95% CI: 0.62, 1.49, with n = 23 exposed cases; *stricter case definition* – HR: 0.76; 95% CI: 0.30, 1.93, with n = 5 exposed cases)	Moderate